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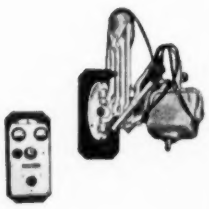

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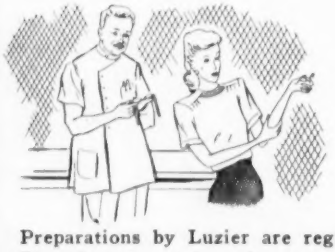

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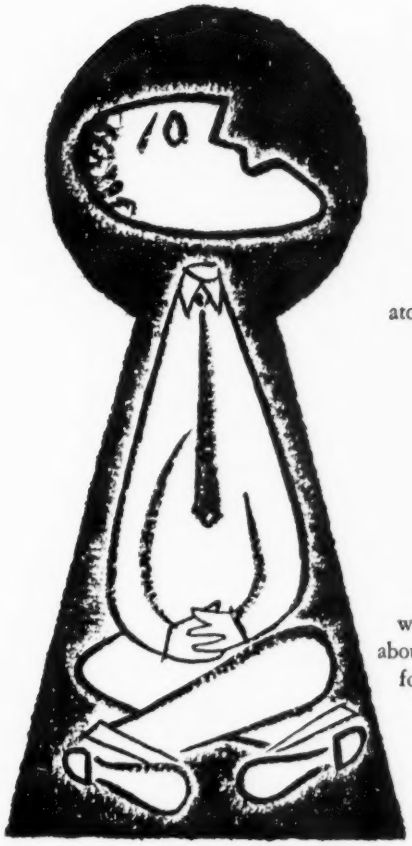

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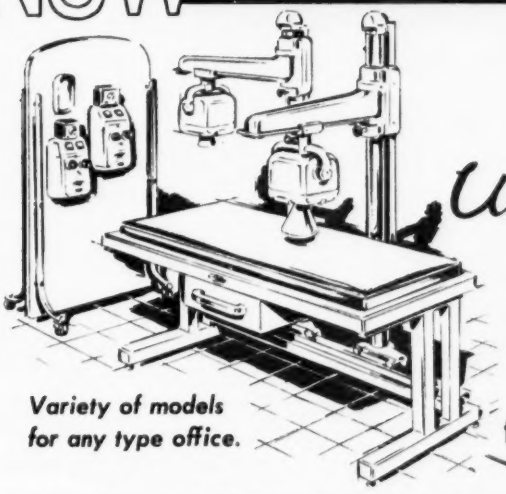

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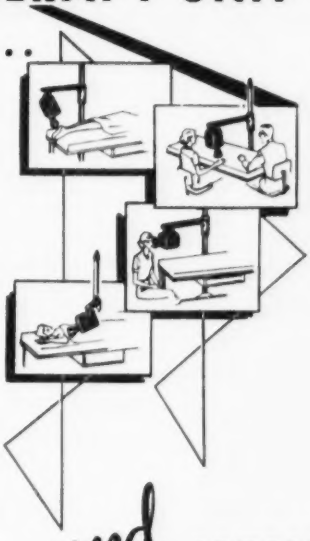

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TISSUE CULTURE STUDIES ON HUMAN SKIN

V. Conjoint Culture of Candida Albicans, Human Skin, and Embryonic Chick Heart; Inhibitory Effects of Endomycin, Candicidin A, and Asterol on C. Albicans Grown Conjointly with Human Skin and Embryonic Chick Heart

FUNAN HU, M.D.
CLARENCE S. LIVINGOOD, M.D.
DETROIT
PATRICIA JOHNSON, B.S.
AND
CHARLES M. POMERAT, Ph.D.
GALVESTON, TEXAS

IT IS WELL known that the available in vitro methods * for testing the fungicidal and fungistatic properties of chemicals and drugs tend to be somewhat inaccurate in that there is not close correlation between laboratory and clinical results. Obviously, one factor which seems to be important in this regard is the fact that to a considerable extent the clinical effect of the therapeutic agent depends on its capacity to penetrate keratin. However, it is possible that other factors (such as enzyme systems which may interfere with the in vivo effect of the fungicide) are involved. Therefore, in order to improve the laboratory methods of testing fungicides, it is important to attempt to duplicate in vivo conditions.

In 1939 Moore,[17] using the embryonated egg technique which was first described by Wolff and Israel [18] and developed by Goodpasture [19] and his associates, reported the successful inoculation of the chorioallantoic membrane with fungi. In a subsequent paper, Moore [20] extended this work and reported on the lesions of the chorioallantoic membrane which were produced by inoculation of numerous organisms, including the common pathogens Candida albicans, Trichophyton gypseum, Epidermophyton inguinale, Microsporum lanosum (canis), and other species of fungi. C. albicans produced lesions which were described as diffuse to confluent grayish opaque plaques; he stated that microscopically "there was active proliferation of the ectodermal cells [of the membrane] with an infiltration of leukocytes, monocytes, and red blood cells, some in various stages of degeneration." This was interpreted as a marked response to the foreign organism. An interesting feature of this reaction

Present address of Drs. Hu and Livingood: Henry Ford Hospital.

Read at the meeting of the American Dermatological Association, Lake Placid, N. Y., June 10, 1953.

Supported by grants from The Upjohn Company; Smith, Kline & French Laboratories, and Hoffmann-LaRoche, Inc.

From the Department of Dermatology (Clarence S. Livingood, M.D., Director) and the Tissue Culture Laboratory (Charles Pomerat, Ph.D., Director), University of Texas School of Medicine.

* References 1 through 16.

was the formation of many whorls of actively proliferating ectodermal cells extending into the mesoderm. Moore described this as analogous to a section of human epithelium which had been invaded with C. albicans. In these embryonated egg preparations, maximum growth of the organism occurred in about four to seven days, and at the end of six days the embryos were dead.

Reid [23] employed a similar embryonated egg technique for testing the fungicidal activity of endomycin and other fungicides. The end point which he used in his experiments was the survival or the death of the inoculated embryos. He reported that a concentration of 50 γ per egg of endomycin resulted in survival of 73% of the infected eggs (compared with a 100% mortality of control infected eggs not protected with the fungicide), whereas a concentration of 10 γ per egg resulted in a survival rate of only 44%. He concluded that the embryonated egg system provided a method for increasing the specificity of the testing of fungicides in that the presence of living tissue tended to duplicate the conditions which prevail in the case of infection in man.

As far as we know, Pomerat † was the first to report the concomitant cultivation of a fungus (two different strains of Penicillium notatum) and living tissues (embryonic chick spleen and heart) in a tissue culture preparation. Heparinized rooster plasma and a 12 to 15% extract of chick embryos were used in hanging-drop tissue culture preparations. He reported that one strain of P. notatum (white) did not cause injury of the embryonic tissue cells, but that the other strain (green) effected restriction of the migration rate of the tissue cells, "rounding up" of cells, and the inhibition of accumulation of fat globules in the cells.

Duque [24] has reported the results of the cultivation of several pathogenic fungi with fibroblasts grown in vitro. The tissues used in his experiments included the spleen of the rat and embryonic chick heart. He reported that yeast cells of Histoplasma capsulatum were found intracellularly in the fibroblasts and that Microsporum lanosum produced a microscopic granuloma characterized by lengthening of the fibroblasts and rounded cells.

Randall and McVickar [25] have reported the experimental cultivation of H. capsulatum in tissue cultures of horse and chick embryonic tissue. They used horse ammoallantoic membrane and placenta and 12-day chick embryo muscle. The horse tissues were cultivated in flasks and on coverglasses placed in test tubes; the chick embryo tissue was cultivated only on coverglasses. In the flask cultures of placenta and ammioallantoic membrane, they found numerous yeast cells of H. capsulatum multiplying within the interstices of the connective tissue, but they did not find any intracellular yeast cells. In the coverglass preparations, scattered throughout the plasma clot, they noted many encapsulated yeast cells surrounded by a well-defined, sharply delimiting membrane. In addition, stained preparations of the chick embryo and horse placenta tissue grown by the coverglass method revealed numerous intracellular yeast cells in scattered fibroblasts throughout the preparation. However, the infected cells (fibroblasts) did not show any signs of degeneration. The authors emphasized that only free individual yeast cells were seen in the supernatant of the flask cultures, whereas intracellular involvement of the fibroblasts was evident when the inoculated yeast cells were fixed in situ and surrounded by clotted plasma.

† References 22 and 23.

In this paper, we shall report our observations of the concomitant culture of C. albicans and human epithelium in hanging-drop tissue culture preparations and the concomitant culture of C. albicans with embryonic chick heart. In addition, we shall tabulate our results in a series of experiments which involve the addition of endomycin, candicidin A, and Asterol (2-dimethylamino-6-[beta-diethylaminoethoxy]-benzothiazole) to the tissue culture medium, to the conjoint C. albicans and human skin cultures, and to the conjoint C. albicans-embryonic chick heart cultures. We shall comment on the interrelationship between the Candida and the living tissue explants and the possible application of this technique as a modality for testing antifungal agents. This method will be compared with the in vitro Burlingame-Reddish technique.[1]

MATERIALS AND METHODS

Fungus Cultures.—The four strains of C. albicans employed were transplants of pure cultures which were isolated from clinical cases of cutaneous moniliasis. They had been maintained in the laboratory on Sabouraud's dextrose agar medium. Suspensions of the organisms were prepared by first making a nine-point inoculum on the surface of the Sabouraud's dextrose agar slant in the Wilson culture bottle,[26] which was incubated at room temperature for a period of four days. At the end of this time there was a colony approximately 4 to 5 mm. in diameter at the site of each of the nine inocula. These colonies were flushed off the surface with 1 ml. of sterile distilled water, and the suspension was removed from the culture bottle by pipettement. The inoculum which was used in the tissue culture experiments was a 1:10 dilution of this suspension. This material was maintained at refrigeration temperature; each week a fresh suspension was made to insure uniformity of the inoculum.

Fungicidal Drugs.—The three antifungal agents studied were as follows: (1) endomycin (Research No. 9706, Upjohn); (2) candicidin A (supplied by Dr. Selman Waksman); and (3) Asterol dihydrochloride (507201, No. 26, Hoffmann-LaRoche). The stock solution (aqueous) of endomycin was 5%; that of candicidin A, 1%, and that of Asterol, 4%; water was the only solvent which was used in these experiments.

Cultivation of C. Albicans in Tissue Culture Medium With and Without Tissue Explants.—Adult human skin explants were cultivated in vitro by the method which we have described in previous publications.‡ The culture medium consisted of a plasma clot made up of 1 drop of heparinized rooster plasma and 1 drop of embryonic chick extract with 4 drops of malignant human ascitic fluid as the fluid nutrient phase of the system. The cultures were made as hanging-drop preparations, sealed with hot paraffin, and incubated at 37 C. One minor change in the procedure (as compared with our previous technique) was the substitution of neomycin (160 γ per milliliter of medium) for penicillin as an antibacterial agent. This was done because the antibacterial spectrum of neomycin is broader than that of penicillin; it is unusually nontoxic for cells in tissue culture[29]; it is stable at room and incubation temperature for an indefinite period of time, and it does not deteriorate on storage.

The technique for the cultivation of embryonic chick heart was identical to that described for human skin except that the ascitic fluid was not included in the system, and therefore the culture medium consisted only of the plasma clot. The heart explants were obtained from chick embryos which had been incubated for a period of six to eight days.

A tiny inoculum of the suspension of C. albicans was introduced into the system after the tissue explant of human skin or embryonic chick heart was planted in the plasma clot. In the case of the skin culture experiments, the inoculation of C. albicans was made before the addition of ascitic fluid. The small (almost invisible) inoculum of the thoroughly mixed 1:10 suspension of C. albicans was carried on the tip of a platinum wire which had been dipped into the suspension; it was deposited on the clot about 1 to 2 mm. distant from the tissue explant.

In another series of experiments, C. albicans was cultivated in the tissue culture medium (with and without ascitic fluid) in the same manner except that the tissue explants were not included in the system.

‡ References 27 through 29.

Finally, endomycin, candicidin A, and Asterol were incorporated in the plasma clot in various concentrations, as described in a previous publication.[27] In one-half of these experiments, tissue explants of human skin or embryonic chick heart were included in the preparations, and in the other experiments of this series, the C. albicans was cultivated in the tissue culture medium without the presence of tissue. The concentrations of these drugs in terms of micrograms per milliliter which were necessary to cause varying degrees of inhibition (slight injury to complete inhibition) of the yeast were determined in each case; in addition, increasing concentrations of the antifungal agents were added until regrowth of the organism did not occur when transplants of the culture to Sabouraud's medium were done.

The cultures were examined at daily intervals for a period of four days, and at the end of that time some of the preparations were opened and transplants to Sabouraud's dextrose agar were made in order to determine the viability of the organisms following exposure to the effect of the drug. These transplants were examined daily for seven days and then at weekly intervals for three to six weeks. If there was no growth at the end of three weeks, the results were tabulated as negative.

Modified Fungistatic Test of Burlingame and Reddish.—This standard in vitro fungistatic test [1] was used in order to compare the results with the data which were accumulated with the tissue culture in vitro experiments. Various concentrations of the antifungal agents were incorporated in Sabouraud's dextrose agar, using the Wilson culture bottle,[28] which contained a slant of about 8 ml. of the medium. The undiluted suspension or a 1:10 dilution of the suspension of C. albicans was streaked on the agar slant with a cotton swab which had been dipped in the suspension. The cultures were maintained at room temperature and were examined daily for the first week and weekly for the next three to six weeks. The majority of the cultures, particularly those with only one or two colonies, which might have represented air contamination, were identified with the use of the cornmeal medium technique, as described by Kligman.[30]

The pH of the media was maintained at approximately 7 so as to duplicate the pH of the tissue culture system. The addition of candicidin and endomycin did not change the pH of the Sabouraud's dextrose agar medium, but the addition of Asterol resulted in a final pH of 5.4. In another set of experiments, using endomycin as the antifungal agent, 10% human malignant ascitic fluid was incorporated in the medium. Finally, the moniliostatic capacity of endomycin was determined under varying hydrogen ion concentration conditions, including a pH of 7.5, 7, 6.1, and 5.2.

RESULTS

Growth of C. Albicans in the Tissue Culture Media.—The growth of the organism was evident in 24 hours and continued until the fourth day, at which time it reached a maximum and became more or less stationary, possibly because of the exhaustion of nutrients. The type of growth (Figs. 1 and 3) was not unlike that which is observed when C. albicans is cultivated on cornmeal agar medium except that there was a larger percentage of spore elements and chlamydospores were not noted.

There was no appreciable difference in the growth of the C. albicans in the tissue culture medium with and without the ascitic fluid phase. The presence of the fluid seemed to result in the extension of the inoculum into many small colonies rather than one single large colony, which was noted in the semisolid plasma clot. Also there was a questionable increase in mycelial elements in the medium which contained the ascitic fluid. At this point it is well to note that chlamydospores were not noted in any of these tissue culture preparations.

Conjoint Culture of C. Albicans and Tissue Explants.—The growth of the yeast organism was identical with that recorded for the cultivation of C. albicans in the tissue culture medium without the tissue explant except that it was more profuse and there was a definite increase of mycelial elements (Figs. 2, 4, and 18) with a corresponding decrease of yeast forms when compared with the growth pattern in the tissue culture medium without the tissue explant.

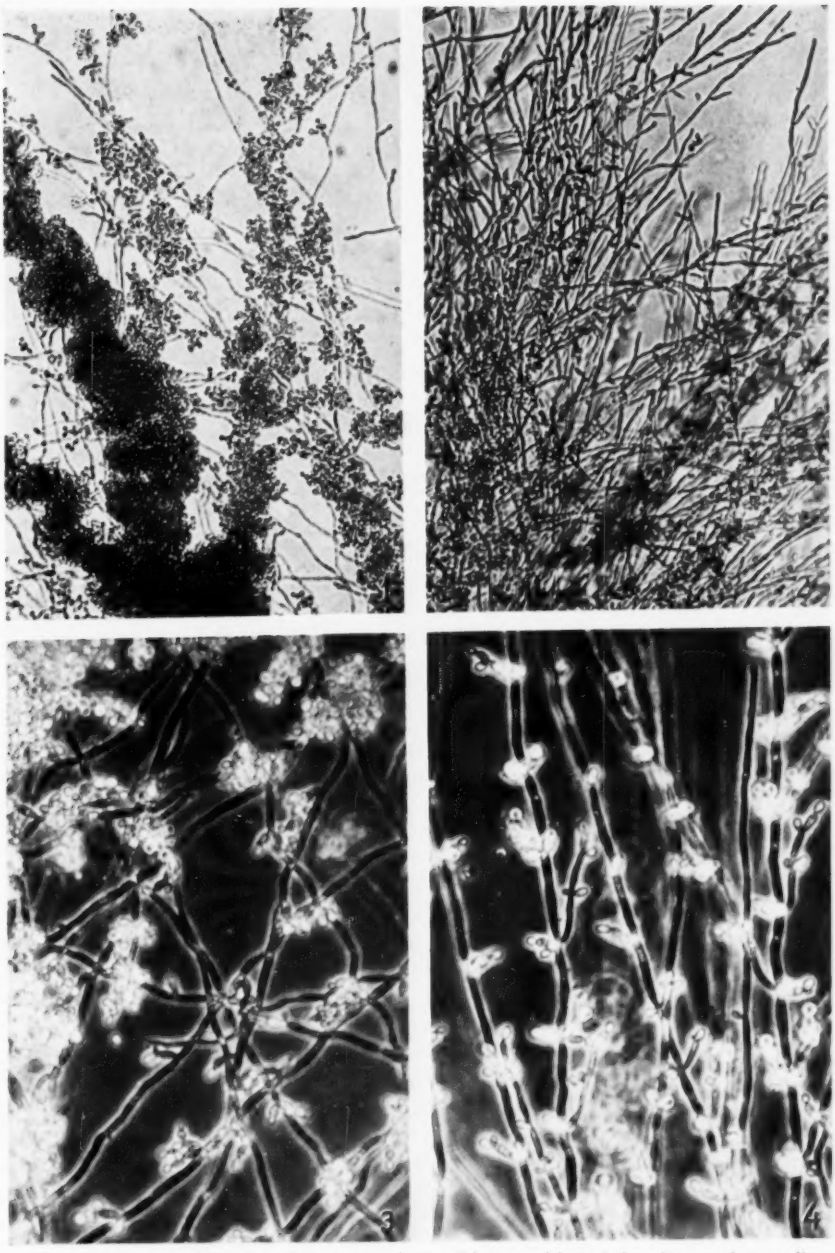


Fig. 1.—Characteristic growth pattern of C. albicans cultivated in plasma clot medium without tissue; × 166.

Fig. 2.—Characteristic growth pattern of C. albicans in plasma clot medium in the presence of a tissue explant; × 166; note the presence of more mycelial elements and fewer yeast forms.

Fig. 3.—Higher magnification of Figure 1; × 333 (dark-phase contrast microscopy).

Fig. 4.—Higher magnification of Figure 2; × 333 (dark-phase contrast microscopy).

Fig. 5-8.—Embryonic chick heart tissue (not shown).

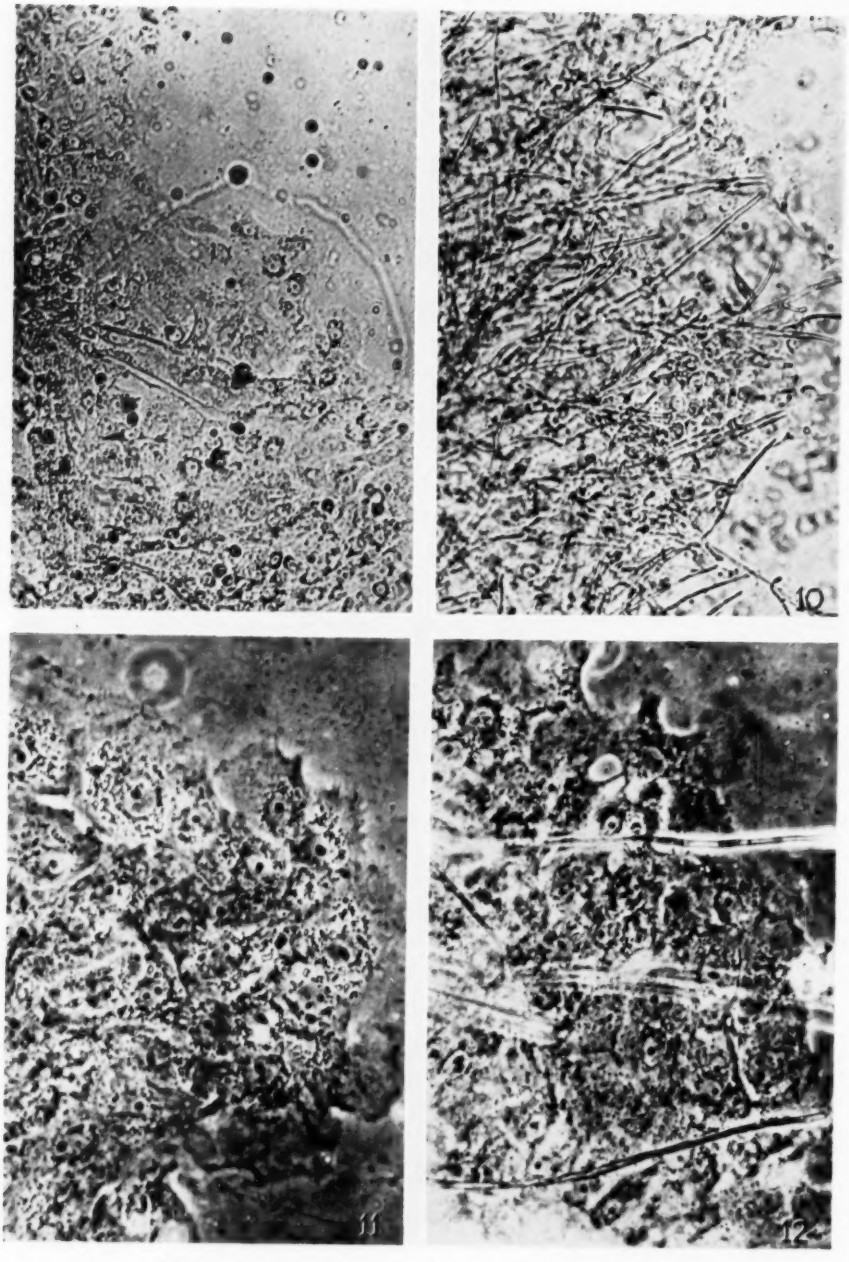


Fig. 9.—Control adult human skin growth in vitro; × 166.

Fig. 10.—Control human skin grown in vitro with C. albicans; × 166. No apparent injury from C. albicans was observed except for deterioration of skin culture after fourth day.

Fig. 11.—Control adult human skin grown in vitro; × 333 (dark-phase contrast microscopy).

Fig. 12.—Control human skin growth in vitro with C. albicans; × 333 (dark-phase contrast microscopy). No apparent injury from C. albicans was observed except for deterioration of skin culture after fourth day.

The concomitant culture of the C. albicans with the human epithelial cells (Figs. 2, 4, 9, 10, 11, and 12) or with the chick embryonic heart tissue (Figs. 5, 6, 7, and 8) resulted in no apparent injury of the tissue. Indeed, it seemed to have no effect (including observation of cell movement as recorded cinematographically) except that the cultures of human epidermis began to deteriorate on approximately the fourth or fifth day rather than the sixth or seventh day, the sequence of events which is usual when skin is cultured without the presence of C. albicans. This deterioration was manifested by degeneration and rounding of the epithelial cells, as well as by some retraction of the outgrowth.

The growth of the C. albicans when cultivated conjointly with embryonic chick heart was similar to that noted with the conjoint culture of the yeast and human epidermis except that there was no acceleration of the deterioration of the chick heart culture. In this regard it is well to note that the control embryonic chick tissue preparations cultivated without C. albicans reached maximum growth within 48 hours and then deteriorated within the next two days.

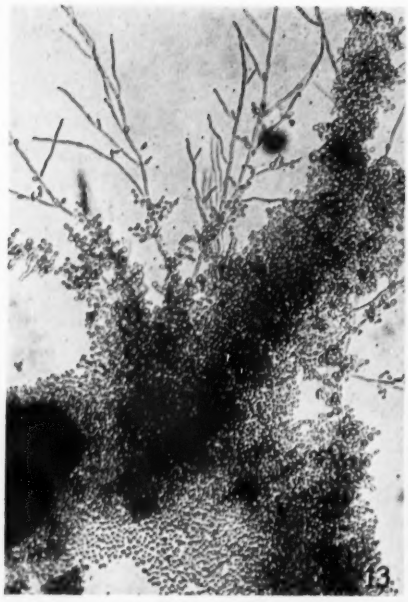
TABLE 1.—*Comparative Toxicity of Asterol, Candicidin, and Endomycin on Tissue Explants in Vitro*

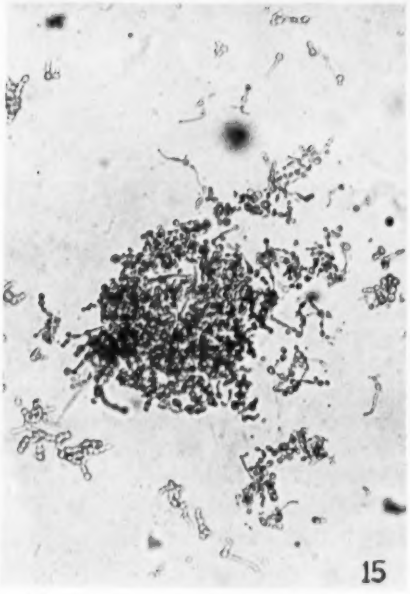
Drug	Tissue	Concentration, in γ per Ml. Culture Media	
		L. I. D.*	M. I. D.†
Asterol	Chick heart	40-80	480-800
	Human skin	20-40	205-830
Candicidin	Chick heart	40-80	100-200
	Human skin	20-40	80-165
Endomycin	Chick heart	100-200	625-1,250
	Human skin	50-100	250-500

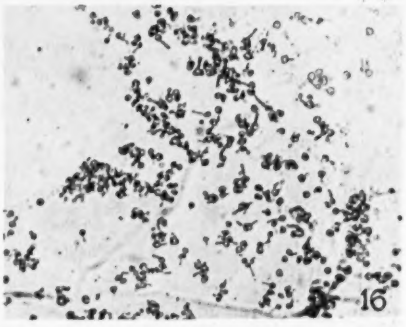
* L. I. D.—least injurious dose when compared with controls.
† M. I. D.—minimal inhibitory dose (complete inhibition).

Effect of Asterol, Endomycin, and Candicidin A on the Growth of C. Albicans Cultivated in Tissue Culture Medium With and Without Tissue Explants of Human Epithelium and Chick Embryonic Fibroblasts.—The comparative toxicities of Asterol, candicidin A, and endomycin for explants of human skin and embryonic chick heart tissue are summarized in Table 1. As explained in one of our previous publications,[28] the L. I. D., or least injurious dose, expressed in micrograms per milliliter of culture medium, refers to that concentration of the drug which causes very slight injury and retardation of outgrowth when compared with control preparations. The term M. I. D., or minimal inhibitory dose, refers to that concentration which causes marked to complete inhibition of growth.

The effectiveness of these drugs as moniliostatic agents was measured by determining the amount of the chemical or antibiotic which was required to cause varying degrees of inhibition of the organism. The first sign of such inhibition was a decrease (Fig. 13) in the number of mycelial elements. Increased concentrations of these antifungal agents resulted in more pronounced decrease (Fig. 14) in the number of branching mycelial and budding forms, decrease in the size of the colony (Figs. 15 and 16) when compared with controls, and clumping of the inoculum. Complete inhibition of growth (Fig. 17) was defined as the complete absence of mycelial forms, with the persistence of only a few yeast-like elements comparable to the size of the







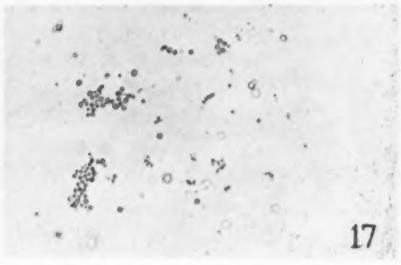


Fig. 13.—Very slight inhibition of growth of C. albicans in skin tissue culture preparation due to addition of 6 γ per milliliter of endomycin; × 133.

Fig. 14.—Slight inhibition of growth of C. albicans in skin tissue culture preparation due to addition of endomycin; × 133.

Fig. 15. Moderate inhibition of growth of C. albicans in skin tissue culture preparation due to addition of endomycin; × 133.

Fig. 16.—Marked inhibition of growth of C. albicans in skin tissue culture preparation due to addition of endomycin; × 133. Note "hand mirror" forms.

Fig. 17.—Complete inhibition of growth of C. albicans in skin tissue culture preparation due to addition of 25 to 50 γ per milliliter of endomycin; × 133.

original inoculum. Under these circumstances of very marked or complete inhibition of growth, the presence of the so-called "hand mirror" forms (an isolated yeast-like cell with a short stump (Figs. 16 and 17) was noted. The photographs (Figs. 13, 14, 15, 16, and 17) which demonstrate these varying degrees of inhibition of growth of C. albicans illustrate the sequence of events which occurred when increasing concentrations of endomycin were incorporated in the plasma clot of conjoint tissue culture preparations of the yeast and human epidermis.

Relatively low concentrations of all these antifungal agents resulted in slight but appreciable degrees of inhibition of the C. albicans (Table 2). In all cases this

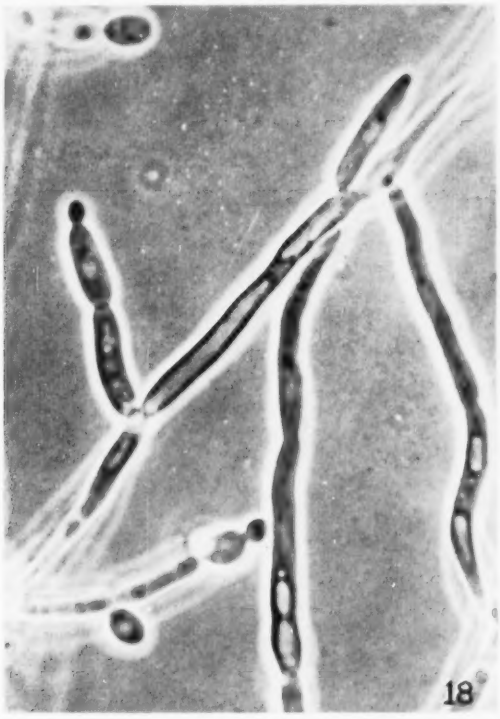


Fig. 18.—Spores and hyphae in various stages of growth as seen typically in skin tissue culture preparation; approximately × 1,500 (dark-phase contrast microscopy).

concentration was less than the amount of the drugs which caused slight but significant injury to the tissue explants (L. I. D., Table 1). The concentrations of all these antifungal agents which resulted in marked to complete inhibition (Table 2) was less than the so-called M. I. D., or amount of the drug which caused complete inhibition (Table 1) of the tissue explants. In the conjoint skin and C. albicans preparations, endomycin and candicidin A were approximately as moniliostatic (Table 2) as they were in the tissue culture preparations which did not include the skin explant. Asterol was less effective as a moniliostatic agent when the skin explant was included in the system. Similar results were recorded in the case of the conjoint

chick embryonic heart and C. albicans cultures in that both endomycin and candicidin A had approximately the same moniliostatic effect (Table 2) with and without the presence of the tissue explants, whereas Asterol had a very definite increased moniliostatic effect when the tissue explants were not included. These results were repeated in many different experiments, and it would seem that they are of statistical significance. It is interesting to note that the type of tissue explant did not influence the moniliostatic effect of endomycin, that the moniliostatic effect of candicidin was definitely more pronounced with the chick heart preparations, and that there was some difference with Asterol in that it was a little more effective when the tissue explant was chick heart rather than human skin.

Concentrations of these drugs which were considerably higher than that required for marked to complete inhibition were not moniliocidal as evidenced by the fact

TABLE 2.—*Effect of Asterol, Candicidin, and Endomycin on C. Albicans in Tissue Culture*

Tissue	Drug	Growth of C. Albicans		Postive Subculture When Transferred to Sabouraud's Medium†
		Very Slight Inhibition	Marked to Complete Inhibition	
Skin	Endomycin			
	With tissue	6*	25-50	100
	Without tissue	6	25-50	25
	Asterol			
	With tissue	10-20	160-400	400
	Without tissue	10	80-160	160
	Candicidin			
	With tissue	1.25	40-80	800
	Without tissue	4	40-80	400
Heart	Endomycin			
	With tissue	5	25-50	60
	Without tissue	5	25-50	25
	Asterol			
	With tissue	10-20	80-160	480
	Without tissue	10	10-20	10
	Candicidin			
	With tissue	1-2	10-20	160
	Without tissue	2	10-20	160

* Concentration of drugs expressed in micrograms per milliliter of medium.
† Concentrations of this order of magnitude were not moniliocidal in that the organism was recovered on subculture. Higher concentrations resulted in negative subculture.

that the organism was recovered on transfer to Sabouraud's medium after four days of exposure to the drug in the tissue culture medium. These results are summarized in the third column of Table 2.

Results of in Vitro Tests Using the Burlingame-Reddish Method.—Concentrations of Asterol as high as 100 γ per milliliter did not suppress the growth of C. albicans for as long as 24 hours, and, furthermore, a concentration of 2,000 γ per milliliter of this antifungal agent did not suppress the growth of the organism for as long as 72 hours. It was quite obvious that Asterol was comparatively ineffective as a moniliostatic agent when it was incorporated in Sabouraud's dextrose agar medium.

Ten micrograms of candicidin per milliliter of medium completely inhibited the growth of the organism for a period of four days, but the concentration which was

necessary for complete suppression of growth for 21 days was 200 γ, and in some cultures there was very slight growth on the 21st day even with this relatively high concentration of the antibiotic.

Endomycin was found to be a more effective moniliostatic agent in the Sabouraud's dextrose agar medium than candicidin. When the pH of the medium was 7,

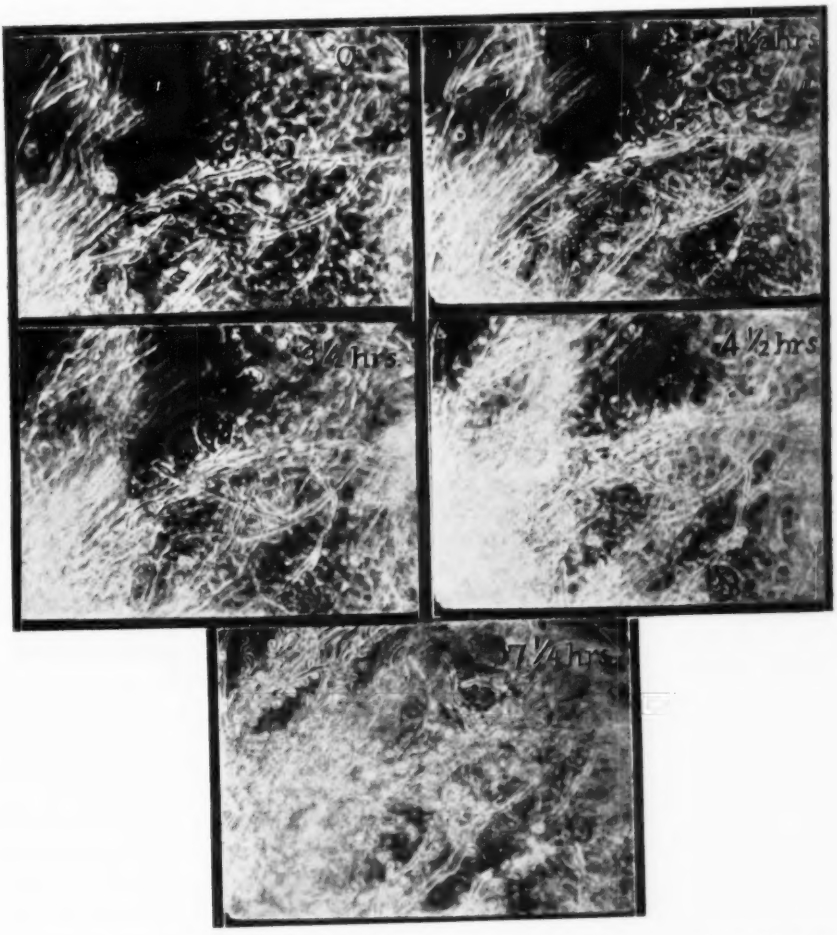


Fig. 19.—Cinematographic records which revealed relatively rapid movement of the bodies within the mycelial elements. Note the rate of growth during a period of seven and one-fourth hours' observation recorded by time-lapse movies.

a concentration of only 1 γ per milliliter suppressed the growth of the yeast for 10 days, and a concentration of 5 γ per milliliter was completely moniliostatic for three weeks, at which time the tubes were discarded. The moniliostatic effect of endomycin was decreased slightly when the pH was 5.2 instead of 7 and also when 10%

ascitic fluid was added to the medium. However, even under these circumstances, this concentration of 5 γ per milliliter of medium resulted in complete inhibition of growth.

CINEMATOGRAPHIC STUDIES

In connection with the present research, approximately 300 ft. of 16 mm. moving picture film utilizing phase-contrast microscopy at medium and high magnification was prepared. Sequences included the growth of C. albicans as seen with an acceleration of 120 times (taken at 8 frames per minute) and of 960 times (1 frame per minute), the natural rate. In some sequences it was noted that the yeast overgrew the entire zone of epidermal cell emigration (Fig. 19). The mobility of epithelial cells, which was observed until they were entirely covered, suggests that at least during four days of observation, under the conditions of the experiment, the epithelium was not damaged. With the use of a perfusion chamber, candicidin (500 γ per milliliter) introduced in the perfusate was not found to influence the activity of the growing hyphae of Candida, but at 2,500 γ per milliliter evidence of marked injury occurred, not only to the yeast but also to human epidermal cells in experiments in which conjoint cultures were employed. However, subculturing of cultures treated in this manner revealed that the Candida remained viable even after 24 hours of contact with 2,500 γ per milliliter of candicidin, but it seemed evident that the epidermal cells were killed.

COMMENT

The problem of cultivating fungi conjointly with human cells carries as a primary requirement that the plant form can proliferate on the medium which meets the minimal requirement for successful outgrowth of tissue cells. Secondly, it is highly desirable to employ fungi and animal cells whose growth rate is such that one species does not overrun the medium before the other has had a chance to obtain a foothold. Our experience indicates that the conjoint culture of C. albicans with human epithelium (as well as with chick embryonic heart tissue) meets these requirements. However, it is possible to add rapidly growing fungi to cultures of human cells after these have shown successful initial outgrowth. In some instances it may be possible to improve the balance of cell systems with growth rates by controlling the incubator temperature.

It is of interest that C. albicans grew side by side with either human skin (for the first four days) or embryonic chick heart explants without apparent injury either to the yeast or to the tissue. However, the presence of the tissue did result in an increase in mycelial elements; perhaps this was due to lowered oxygen tension incident to the additional nutritional requirements of the explants. It may be significant that there was definite acceleration of deterioration of the skin cultures after the fourth day when they were cultivated conjointly with the yeast. It is conceivable that toxic products elaborated by C. albicans were responsible for this sequence of events. On the other hand, this premature deterioration of the epithelial explants might have been due to the simple fact that there was competition between the organism and the tissue explant for the nutrient material in the tissue culture medium of the hanging-drop preparation.

It is probable that there is a wide variation in the effects of various species of pathogenic fungi on tissue culture explants of skin and other tissues. Pomerat §

§ References 22 and 23.

found that one strain of P. notatum caused injury of embryonic chick spleen and heart in the tissue culture preparation, whereas another variant of the same organism did not cause such injury. We are planning to study the effects of other pathogenic fungi on human skin in conjoint tissue culture preparations. Furthermore, the use of the roller tube tissue culture technique would make it possible to study the effects of the fungus (and its products) on the tissue explants over a longer period of time.

In the tissue culture experiments, Asterol was many times more effective as a moniliostatic agent than in the more artificial Sabouraud dextrose agar medium, whereas both candicidin and endomycin were far less effective in the tissue culture preparations than they were in the tests done with the Burlingame-Reddish method.

Another interesting finding in these experiments was the fact that the concentrations of the antifungal agents which were completely inhibitory did not prevent growth of the organism when transplants were made to Sabouraud's dextrose agar medium. For example, in the human skin-C. albicans cultures, candicidin effected complete inhibition of growth when the concentration was of the order of 40 to 80 γ per milliliter, but a concentration of 2,500 γ per milliliter for a period of 24 hours did not prevent regrowth of the organism when a transplant of the culture to Sabouraud's medium was done.

There are several sources of experimental error to be considered in the interpretation of these results. In the first place, only a very small fragment of the culture was transferred, and it is possible that other fragments would have been positive on subculture. Another source of error which would lead to a negative culture despite the fact that the organism had not been killed is the possible transfer of the antifungal agent along with the inoculum. With these reservations in mind, it is interesting to note that there was comparatively little difference between the moniliostatic and moniliocidal concentrations of endomycin, whereas there was a wide range between the apparent moniliostatic and moniliocidal concentrations of candicidin. In the tissue culture preparations, the presence of the tissue explants had a very pronounced effect on the moniliostatic and moniliocidal properties of Asterol; for example, with the embryonic chick heart cultures, more than 480 γ per milliliter of Asterol was necessary for a moniliocidal effect in the presence of the explant, but a concentration of only 10 γ per milliliter prevented regrowth on transplanting to Sabouraud's medium when the explant was not included in the preparation. The data which we have accumulated to date do not make it possible to form even a preliminary opinion as to the possible application of this technique for the evaluation of antifungal agents. However, it would seem worth while to continue these studies.

The cinematographic phase of this study leads to the important suggestion that the interplay between human cells and various species of saprophytic and pathogenic fungi can be observed directly, with the further advantage that nutrients and drugs, such as fungicidal agents, can be introduced. Thus the relations of forces operating in parasitic infections may be described in the living state, together with the modifications in host-parasite cell activity produced with the introduction of therapeutic agents.

SUMMARY

Candida albicans was cultivated in a tissue culture medium consisting of a plasma clot made up of 1 drop of heparinized rooster plasma and 1 drop of embryonic chick extract; in some experiments 4 drops of malignant human ascitic fluid was added to the system.

With use of the same medium in a hanging-drop preparation, explants of human skin and embryonic chick heart were cultured conjointly with C. albicans.

The minimal inhibitory dose (M. I. D.) and least injurious dose (L. I. D.) of endomycin, Asterol, and candicidin A were determined for human skin explants and chick embryonic heart explants.

The concentrations of endomycin, Asterol, and candicidin A (micrograms per milliliter of medium) which were necessary to cause varying degrees of inhibition (very slight to complete) of growth of C albicans were determined for the yeast when it was grown conjointly with human skin and chick embryonic heart tissue and compared with the results in control preparations which did not include the explants of skin and embryonic chick heart.

The concentrations of endomycin, Asterol, and candicidin A which were necessary to inhibit the growth of C. albicans in Sabouraud's dextrose agar medium (Burlingame-Reddish technique) were determined.

The type of growth of C. albicans in the tissue culture medium was similar to that observed when the organism was cultivated on cornmeal agar medium; chlamydospores were not formed.

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LOW-VOLTAGE X-RAY THERAPY IN DISEASES OF THE SKIN

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BERYLLIUM tube x-ray units capable of delivering very soft irradiation have come into wide clinical use during recent years. Although a considerable number of reports on the effects of very soft x-rays on various diseases affecting the skin are available, interpretation of papers published prior to 1945-1950 is difficult. Older so-called grenz-ray units were relatively crude pieces of apparatus, with tubes of uneven wall thickness and inadequate means of controlling voltage and amperage precisely. Moreover, the calibrations of output from these units were made by methods which, on the basis of more recent physical studies, may be regarded as highly inaccurate.

Great emphasis has been placed upon the relative safety of very soft irradiation. This emphasis is probably well justified in the case of x-rays generated at 6 or 8 kv.; in fact, if such rays are used in the treatment of skin having a thick layer of stratum corneum, the physiologic effects are probably nil. However, units with low inherent filtration are capable of delivering 1,000,000 r or more per minute at contact distance when operated in higher kilovolt ranges, and are thereby capable of producing disastrous effects if not used with knowledge of the physical characteristics of such units and with the greatest precaution to insure delivery of the calculated dose at the skin target. Moreover, a survey of the various types of units sold and in use since 1945 would indicate that some of them have serious deficiencies of construction in respect to crucial factors, such as accurate control of the kilovoltage at which the x-rays are generated, accuracy of the exposure timer, and of the mechanism for automatic termination of the exposure. As stated above, it is also only within very recent years that competent physicists have come into some measure of agreement as to the adequacy of the methods of calibrating the output of such units.

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Dr. S. Reid Warren Jr., Professor of Radiologic Physics, University of Pennsylvania, was responsible for the calibrations and gave much helpful advice. Joint observation of the patients in this series was made with a number of other physicians, including Drs. Clarence S. Livingood, Malcolm C. Spencer, Hugh M. Crumay, Walter B. Shelley, John J. Laskas, and Charles A. Bikle. Miss Katherine E. Pillsbury assisted in the tabulation of data from the charts of the patients.

It has been the purpose of this clinical study to attempt to determine the effectiveness and safety of very soft x-rays on a variety of dermatoses over a considerable period of years. In part this effort has been stimulated by an increasing conservatism in the use of "standard" superficial x-ray therapy, in which the depth of the irradiation is often many times greater than is required. With such therapy, the field to be exposed is ordinarily carefully outlined and the surrounding skin shielded, but normal tissue 1 or 2 cm. below a localized lesion may receive very considerable amounts of irradiation. This may be regarded as a somewhat obtuse monoplane type of precautionary technique in which the surrounding normal tissue is protected but underlying tissue assaulted, unnecessarily. If one is to give any x-ray therapy to the skin, selection of a proper depth dose would seem to be mandatory.

This study records our results with the use of very soft x-rays in a series of 550 patients treated over a period of six years. In some of the patients, observation of the effectiveness of very soft x-rays has been possible on a controlled basis, namely, that certain comparable lesions were treated and others were not and that follow-up observation was made by a physician who had seen the lesions previously but who was unaware of which sites had been treated. During the past two years, it has been our almost routine custom in the case of skin diseases with multiple sites of involvement, to give the initial treatment to one or two sites only, and this has furnished some measure of control. A particular effort has been made to observe those patients who have received larger amounts of very soft x-radiation for as long a time as possible, in an effort to determine whether or not untoward effects in the skin will develop. Almost all of the patients were seen as private patients, and with very few exceptions have been observed by one of us (D. M. P.). In many of the patients, observation of the effect of very soft x-rays under strictly controlled conditions was not possible, and the results of such therapy must be interpreted in the light of experience with many patients with similar diseases treated by other means.

In reporting this series of clinical observations, we had hoped that it would not be necessary to discuss the physical characteristics of very soft x-rays in any detail. However, it has been difficult to obtain adequate information concerning very soft x-rays from any single source in the literature, and a short summary of the available data seems advisable. It is certain that unless a therapist is entirely familiar with these basic facts and with certain of the more extensive reports available in the radiologic literature, and unless he has had a considerable amount of actual training, he would be well advised not to attempt very soft x-ray therapy with modern "multipurpose" units. However, many such units have been sold for use by individuals with inadequate training.

BASIC CONSIDERATIONS IN REGARD TO THE PHYSICAL CHARACTERISTICS AND BIOLOGIC EFFECTS OF VERY SOFT X-RAYS

Certain simple preliminary statements have been included intentionally in the following summary, in an effort to make the discussion reasonably clear to the reader who has had no experience or training in x-ray therapy.

1. *Varying Quality of X-Rays.*—X-rays are a form of electromagnetic radiation which produces biologic effects in tissue by inducing ionization of the atoms in the tissue. Although the amount and the depth of the ionization may be varied by changing the character of the x-rays, there is no known qualitative difference between the biologic effects of x-rays of widely different quality.

In ordinary practice, x-rays are produced by accelerating electrons from a heated filament (cathode) to impinge on a target (anode). The acceleration occurs as a result of the voltage applied to the tube, usually expressed as kilovoltage. The x-rays produced at any given kilovoltage are not uniform, but are a continuous spectrum of various wave lengths. It is known, however, that the higher the kilovoltage the shorter the minimum wave length (more penetrating) of the rays produced. This is expressed in the formula:

$$\text{Wave length (in A)} = \frac{12.35}{\text{kilovoltage}}$$

The shortest possible wave length with any kv. thus can be calculated readily, but in addition an abundance of longer rays are also produced within the tube. Soft rays, therefore, are always produced along with hard rays. If the hard rays are to be eliminated, it is necessary to operate the tube at a low kv. On the other hand, when only the harder rays are desired, filters are used to remove the soft rays from the beam. It is obvious from this preliminary discussion that by varying the tube window or the filters, widely varying qualities of x-rays may be obtained at the same kv. potential. In describing x-rays, therefore, the nature of the emitted rays must be given rather than the kv. used to produce them. This can be done as "effective wave length" in angstroms, or, more practically, as that thickness of aluminum which will just reduce the intensity of the beam by one-half: the half-value layer (H. V. L.). In a later discussion thickness of "tissue" will be discussed as an additional useful method of describing the quality of x-rays.

2. X-Ray Tubes Which Transmit Soft Rays.—In recent years there has been increasing interest in utilizing longer, less penetrating rays for superficial therapy, so that the desired therapeutic effects might be confined to the involved area and not affect underlying normal tissue. To do this, it has been necessary to devise a means of permitting the softer rays produced within the tube to penetrate the tube wall. In Figure 1, it can be seen that the metal beryllium, with its low atomic number, permits far more of the soft rays to leave the tube than does Pyrex glass.

Earlier tubes designed to permit the use of soft rays were made with Lindeman low atomic number glass windows,[2] but these varied in thickness and were too fragile for use with high kilovoltages. As early as 1929, Glasser reported attempts to prepare a beryllium-window tube,[2] but practical problems of making beryllium with proper qualities apparently were not solved until 1942, when Machlett described his tube.[3]

Because of the long follow-up now possible on patients treated by the early workers, such as Bucky, Glasser,[2] Ebbehøj,[4] and others, with Lindeman window tubes, it would be of interest to compare the radiation from these tubes with present beryllium-window tubes. As was pointed out, the radiation varied considerably with the Lindeman window tubes, and kilovoltage, which is particularly important at low kv. was undoubtedly not always properly controlled. Nonetheless, a comparison made by Ebbehøj,[5] reveals a surprising identity of radiation at 12 kv. and suggests that the data given in earlier studies may be considered roughly equivalent to recent work with beryllium-window tubes in the 12 kv. region. However, it must be kept in mind that individual Lindeman tubes undoubtedly varied considerably in wall thickness.

3. Absorption of Soft X-Rays in Air.—Having solved the problem of getting the soft x-rays out of the tube, it became necessary to study this radiation further.

The absorption of x-rays in air was investigated by Day and Taylor,[6] who concluded that "there is no significant selective absorption of the soft components of the x-rays in traversing the amounts of air considered." This was rather surprising, but, as Jennings [7] clearly explains, the minimum distance Day and Taylor could get to the x-ray source was 119 cm. of air. Having traversed this amount of air, the beam was highly filtered before they could measure it. Jennings, on the other hand, using a 1 mm.-thick beryllium-window tube and a different type of measuring device, demonstrated that by increasing the f.-s. d. (focus-skin distance) there is a hardening of the beam due to air loss, as earlier workers had indicated, and an increase of penetration in addition to that which occurs from the inverse square law effect. Trout and Gager,[8] using a 2 mm.-thick beryllium-window tube, also demonstrated the failure of the inverse square law due to air absorption and the change in quality

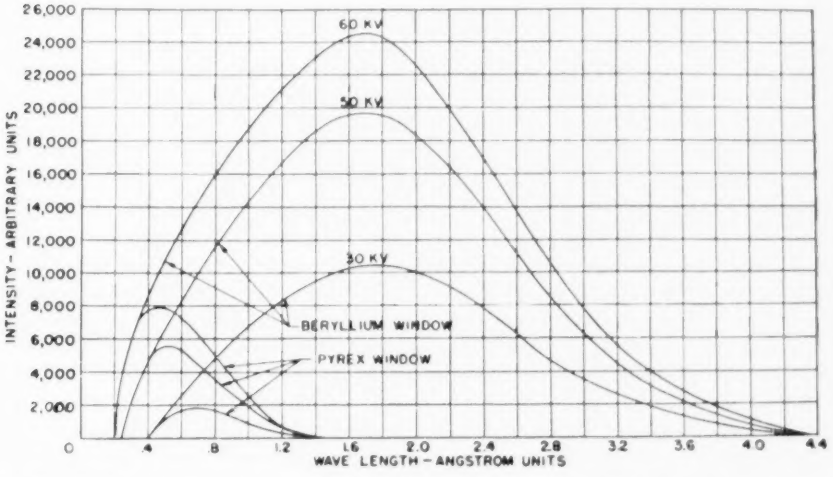

Fig. 1.—Comparison of intensity and quality of irradiation through beryllium and Pyrex windows (from Rogers[1]).

due to air absorption at short distances. It may be concluded, therefore, that the statement of Day and Taylor [6] is valid only when the tube is more than 100 cm. from the object being irradiated. Below this distance, significant absorption of the soft x-rays in air occurs, and calculations based upon the inverse square law alone are not valid.

4. *Measurement of Soft X-Rays.*—One of the most difficult problems in the study and use of very soft x-rays has been an accurate practical method of measuring them. Victoreen, Atlee, and Trout [9] pointed out that the ordinary bakelite thimble chamber used for harder radiation gave very low readings because of the failure of the soft rays to penetrate the chamber walls and be detected. Trout and Atlee,[10] for example, in an early paper (1942) reported measurements of radiation from a beryllium-window tube which Rogers [1] subsequently said were 50% of the actual dosage. He also criticized the beryllium wall chamber measuring device which they

devised to replace the bakelite thimble, because it shows an error of 10% at 1.5 A. Inasmuch as a major proportion of the radiation is at wave lengths greater than 1.5 A. (Fig. 1), errors greater than 10% could be expected.

A number of other devices have been used to overcome the various shortcomings, particularly wave length dependence, of the measuring apparatus. The reference standard for many of the studies is an "open air" chamber in the United States Bureau of Standards, which was reported in 1932 by Taylor and Stoneburner,* but which Glasser [2] apparently had access to before 1929. This chamber, which has been discussed at length by Day,[11] is a "standard guarded field, free air ionization chamber," which permits the measurement of radiation without requiring it to pass through any chamber wall. The free air chamber is not generally available, and furthermore is not suitable for depth dose measurements which are essential for the clinical use of x-radiation. Its great usefulness, therefore, is in the calibration and comparison of other smaller, more flexible instruments. The earliest report of a reasonably satisfactory device is that of Glasser,[2] who made a 1 cc. ionization chamber of goldbeater's skin, which was independent of wave length down to rays produced at 5 kv. when compared with the free air chamber. More recently a commercially available thimble chamber with a nylon wall 0.005 in. (0.013 cm.) thick has been studied by Day,[11] and used by Trout and Gager.[8] If this chamber were used to measure radiation generated at 10 kv. and gave a reading of 100 r, actually 142 r had been delivered; if it were used at 20 kv. and read 100 r, the correct amount would be 132 r. At higher kv. or with added filtration, the correction factors are more linear. Jennings [7] further criticizes this nylon thimble chamber by pointing out that it is less satisfactory than a chamber with a plane surface for depth dose measurements ranging between 0.3 mm. and 1 cm. His own work yielded greater penetration figures than those of Trout and Gager at all points where comparison was possible, indicating that the Victoreen nylon thimble does not detect all of the radiation, particularly requiring correction factors below 0.06 mm., Al H. V. L., or approximately 25 kv.

A variety of other ionization chambers have been reported which attempt to reduce the absorption of the soft rays by using a substance with negligible mass at the spot the rays enter the chamber.† Quimby and Focht devised a chamber with India-ink-coated silk thread mesh; Seemann used Kodapak I, a cellulose acetate sheet 0.00088 in. (0.00224 cm.) thick, and Braestrup used extremely thin nylon films coated with graphite. Jennings compared various instruments, including the Siemens Phantom Chamber and Siemens Grenz-Ray Chamber, which have a 0.03 mm. film of Styroflex plastic coated with graphite, and for radiation below 7 kv. used the grenz-ray chamber with a very fine nylon thread mesh instead of the plastic film. From such studies one may conclude that the most accurate and practical measurements can be made with a chamber which is least likely to be wave length dependent. Reasonably satisfactory and safe results can, however, be obtained with the commercially available Victoreen nylon thimble r-meter, if it is carefully calibrated against a reliable ionization chamber. Ionic recombination is an additional source of error and low readings, which must be guarded against with some devices such as the nylon thimble r-meter, when the dose rate is in excess of 1,000 r per minute.[7]

* Cited by Rogers.[3]

† References 6, 7, and 1.

5. *Relationship of Output to Kilovoltage.*—In addition to the unusual difficulties of measurement of the radiation from beryllium-window tubes at different wave lengths, these tubes present the problem of having a huge difference in output of radiation with small differences in the kv. applied.‡ In Figure 2 it can be seen for example: that with minimum filtration at 10 kv. the surface dose rate is 1,500 r per minute, but at 15 kv. the rate is 4,500 r per minute. Because a change of a few

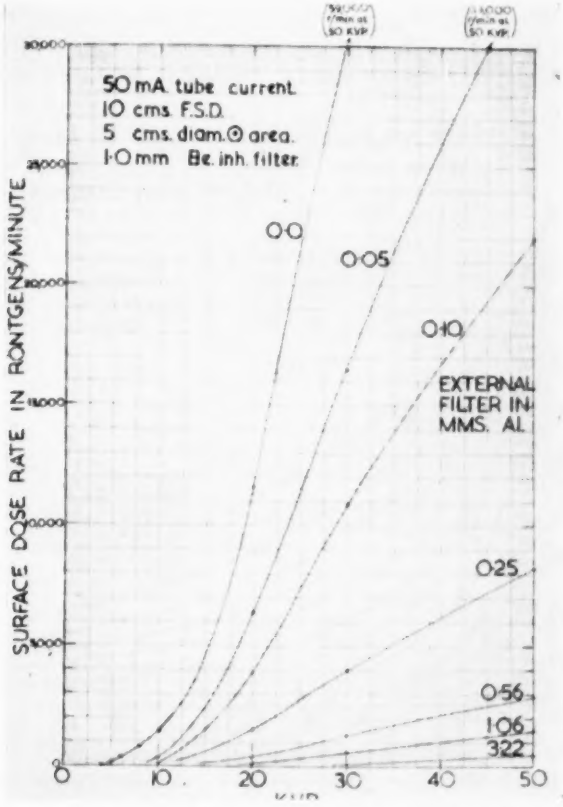

Fig. 2.—Relation of output to kilovoltage at varying filtrations (from Jennings[7]).

kv. can double or halve the dose delivered, it is of the greatest importance that the voltage regulating devices, particularly at low kv. be as accurate and constant as possible.

6. *Measurement of Soft X-Rays in Tissue.*—The H. V. L. in millimeters of aluminum defines the quality of radiation, but it does not give the therapist necessary details of penetration of the rays into tissue. To make the best use of the soft x-rays now easily available with modern beryllium-window tubes, it is necessary to know accurately and quantitatively how much of the surface dose is delivered to the desired

‡ References 7 and 8.

depth in tissue (Fig. 3). Because of the relatively deep penetration of all rays from ordinary glass x-ray tubes, they can be studied quite easily. The large component of soft rays from a beryllium-window tube, however, are appreciably diminished by fractions of a millimeter of tissue, so that special techniques are necessary for obtaining reliable measurements.

Such studies are made by interposing tissue of different thickness between the x-ray source and the measuring chamber and plotting the reduction in radiation intensity against the thickness of tissue. Cipollaro and Mutscheller [12] made such measurements in 1940. Although they took precautions to prevent the drying of their specimens, some of the discussers of their paper felt that it was not possible

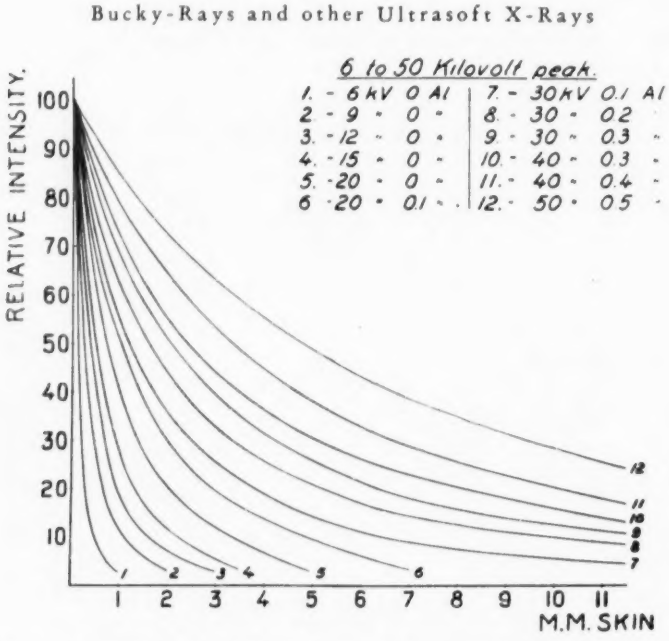

Fig. 3.—Penetration into skin of soft x-rays of varying quality (from Ebbehøj[5]).

to prevent all water evaporation. It also is not clear from their paper whether they used an adequately thin chamber to measure the "grenz" rays produced with a Lindeman window tube at 10 kv.

To simplify the technique of absorption measurements in tissue, Ebbehøj [5] compared absorption curves of a paraffin paper with those of human skin and animal ears. He concluded that they were sufficiently similar to permit him to use waxed paper in his experiments but report the results as millimeters of skin. Jennings [7] investigated the problem and concluded that a solid wax phantom material proposed by Jones and Raine [13] which has absorption characteristics very close to those of water was better than the wax paper and should reflect the results in wet tissues very accurately. Because of the opportunity of preparing uniform films of any

desired thickness and its well defined x-ray absorption characteristics, this material seems to be the best substance available for this purpose. It has the following formula:

Paraffin wax	60.8%
Polyethylene	30.4%
Magnesium oxide	6.4%
Titanium dioxide	2.4%

7. Penetration of Soft X-Rays in Tissue.—The results of the measurements of radiation from modern beryllium-window tubes operated at low kv. are very similar to those reported for the earlier Lindeman window tubes. For the most part data

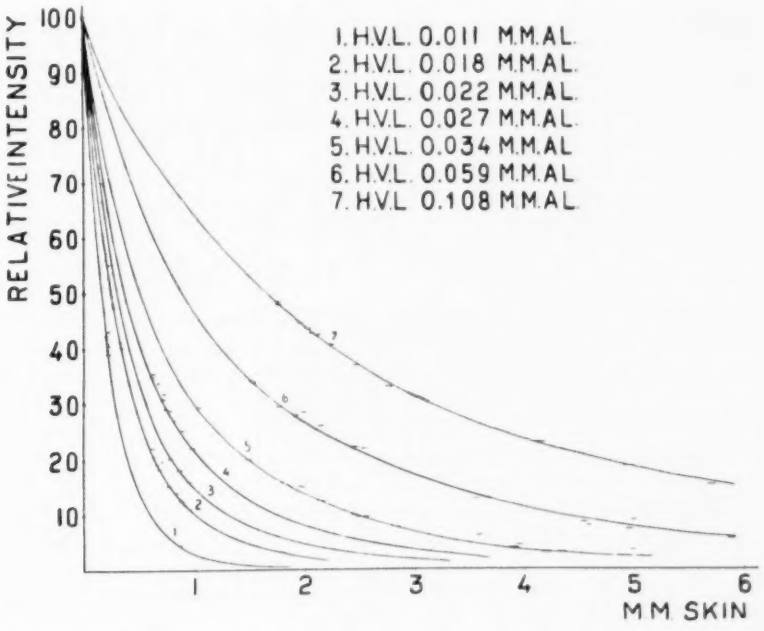

Fig. 4.—Absorption curves indicating relative intensity of radiation at varying depths of the skin (waxed paper) with radiations of different quality (from Ebbehøj[4]).

have been reported in terms of millimeters of skin or tissue with adequate reference to the H. V. L. in small fractions of a millimeter of aluminum. Jennings[7] has introduced a useful new term: H. V. D. (half-value depth) by which he means the depth at which the dose rate is reduced to 50% of that at the surface. It is a measure of the penetration and includes the scatter contributions, thereby depending also on the field area and f.-s. d. (focus skin distance) concerned, whereas the H. V. L. in aluminum is a measure of the radiation quality and is closely related to the emitted spectral distribution as transmitted by the beryllium window.

Ebbehøj's[5] measurements of penetration of soft x-rays in skin (wax paper) are shown in Figure 4. From these curves one can calculate the percentage of radiation at any depth of the skin if the H. V. L. (in Al) of the x-rays is known. It is

of interest to compare the results of three investigations at two significant points. The figures indicate millimeters of skin at which the surface dose is reduced as indicated:

	50%	10%
Cipollaro and Mutscheller (1940)	0.3 mm.	1.3 mm.
Ebbehøj (1952)	0.3 mm.	1.4 mm.
Jennings (1950)	0.35 mm.	1.5 mm.

Trout and Gager [8] have summarized their depth dose data with a 2-mm. beryllium-window tube operated from 30 to 100 kv. in Figure 5. Although Jennings [7] felt that the softer rays penetrate slightly deeper than these results indicate, they

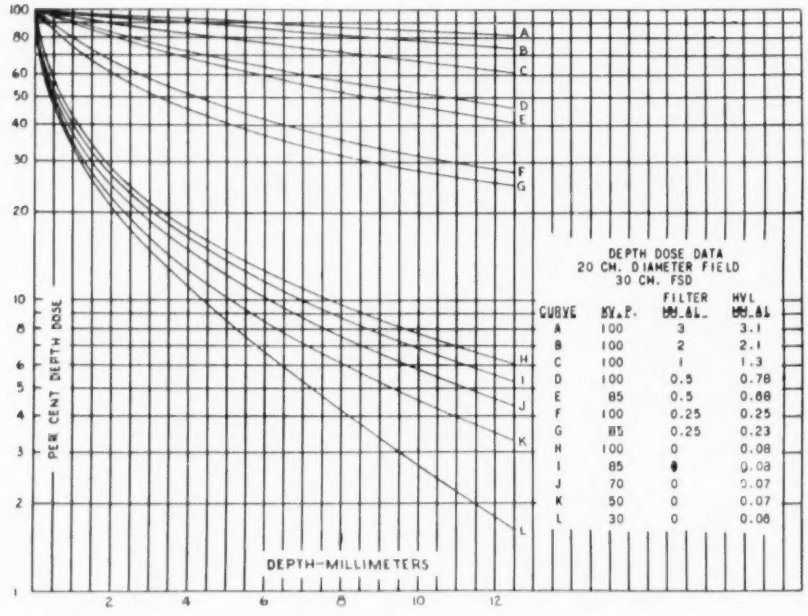

Fig. 5.—Absorption curves in "tissue" of x-rays from a 2.0 mm. beryllium-window tube (from Trout and Gager[8]).

are not seriously inaccurate and reveal several points of interest. They show the wide range in quality of radiation which can be obtained with such a tube. For example, one can have a choice of rays which will be reduced by 50% by a thickness of tissue ranging anywhere from 0.4 mm. to more than 20 mm. In addition, Figure 5 demonstrates the surprisingly small increase in penetration of x-rays when no filters are used and the kv. is increased from 30 to 100. This is also reflected in the small change in the H. V. L. in aluminum (from 0.06 to 0.08 mm.) over this same range. On the other hand, the output of radiation would be enormously increased. Trout and Gager [8] also state that backscatter is no problem until a peak of 70 kv. is reached and then only amounts to 2 to 4%. Other authors are in agreement with this.

8. *Special Precautions with Beryllium-Window X-Ray Tubes.*—With the low atomic number window tubes it is possible to deliver 500,000 to 1,000,000 r or more per minute to the skin at contact distance. One case has been reported of an engineer who inadvertently received 8,000 r on his finger, in a 10-second exposure at 35 kv. and 20 ma., approximately 5 cm. from a Lindeman window tube.[10] Although the original dermatitis healed, the skin broke down two years later and the finger required amputation. Spencer § has reported two incidents in which a "dual range" x-ray unit was inadvertently operated at a kilovoltage much higher than the very soft x-ray range, with resultant severe x-ray sequelae. With this unit, change from the very low kv. range to a higher "standard" range was accomplished by a toggle switch, and the kilovoltage read on the upper scale of the same voltmeter. Such a device is completely unsafe. To prevent similar accidents in clinical practice it is desirable to install fool-proof devices (if such there be) which will prevent the delivery of radiation with a beryllium-window tube when the potential exceeds approximately 15 kv. unless a filter has been inserted.

If the apparatus is to be operated in the full range from 10 kv. to 50 kv. or more, it is essential to have two separate kilovoltage meters, so that an accuracy within 1 kv. can be obtained at the lower potentials. For dependable knowledge of the dose of radiation delivered it is also necessary that efficient voltage regulators be used to maintain the potential within at least 1 kv. during operation. As pointed out before (see Figure 2), slight variations in potential at the lower kv. cause great changes in the output of radiation.

From the discussion of the difficulties of measurement of soft x-rays, it is apparent that accurate and safe calibration of a particular tube and machine requires the use of an ionization chamber which has minimal wave length dependence, and which itself has been properly calibrated against a reliable standard.

Lewis and Mutscheller [14] emphasize the difference in quality of radiation from two different machines operating at the same kv. and state that the apparatus should be calibrated according to the H. V. L. of the beam rather than the kv. indicated on the control panel. The same authors demonstrated the greater reduction of radiation at the edges of the field, as compared with the ordinary Coolidge tube. They also point out the decreased radiation on the anode (target) side of the field producing a "heel" effect. These difficulties can be recognized by measurements over the field at the time of calibration.

9. *Comparison of X-Rays Used for Very Superficial Therapy.*—Grenz ray is a term which Bucky originally used to describe x-rays from a Lindeman window tube operating at 12 kv. or less. Some authors have also referred to this radiation as "Bucky rays."[5] The following definitions of grenz rays appear in the literature:

Glasser[2]: 1 to 3 A; produced at 4-12 kv., H. V. L. of 0.0007 to 0.04 mm. Al
Ebbehøj[5]: H. V. L. of 0.1 to 0.4 mm. of skin
Cipollaro[12]: H. V. L. of 0.036 mm. Al or less
Kalz‖: H. V. L. of 0.034 mm. Al or less

With the wider use of various beryllium-window tubes, however, the term grenz rays has often been used in describing other radiation such as that produced at 30 kv. with a 2-mm. beryllium window, which has a H. V. L. of 0.060 mm. Al. Because

§ Spencer, M.: Personal communication to the authors.

‖ Cited by Lewis and Mutscheller.[14]

of the resulting confusion and difficulty in precise comparison between workers using different definitions of the term, it is considered preferable to refer to this radiation as soft or very soft x-rays and to add the precise limits of the quality of the rays used in terms of H. V. L.

"Contact" x-ray therapy is another form of roentgen radiation designed for very superficial therapy. With the two types of apparatus available, Chaoul and Phillips, the target is at the end, rather than centered within the tube, and the x-rays exit directly through the end of the tube which is placed in "contact" with the lesion to be treated. From inverse-square law considerations it can be shown that the amount of radiation in the depth of the tissue is less than with conventional glass x-ray tubes. The details and results with this form of roentgen therapy for the treatment of accessible cancer are presented in detail by Smithers.[15]

Braestrup and Blatz [16] state that contact therapy machines operating at 44 to 50 kv. and 2 ma. deliver approximately 10,000 r per minute at a distance of 1.8 cm. From their data it is apparent that beryllium-window tubes may be adjusted with regard to kv. and added filtration to deliver x-rays with essentially the same features as from a contact-therapy apparatus.

10. *Biological Aspects of Soft X-Radiation.*—Borak [17] some years ago, stated that the approximate lethal dose of x-rays in a single exposure for cutaneous tissues is as follows:

sweat glands	2500 r
epidermis	2000 r
hair follicles	1600 r
sebaceous glands	1200 r

These figures applied to x-rays from a conventional glass tube, where there is only a relatively small difference between the surface dose and that delivered to the glands of the skin. In any case one may assume that the above figures indicate the amount which has to be delivered to the specific cells rather than merely the surface dose. As Ebbehøj [5] points out, the softer the x-rays used, the less the risk of radionecrosis, because of the enormous increase in penetration which accompanies an increase in voltage and filter value.

Christensen, Sommers, and Spalding [18] studied the effects of x-rays from a 2 mm. beryllium-window tube operated at 100 kv. with no added filter. The radiation has a H. V. L. of 0.08 mm. Al. The 50% depth dose is approximately 0.8 mm. of tissue and the 10% depth dose is approximately 8.0 mm. of tissue. In the rabbit skin they saw no erythema at 1,390 r but beginning erythema at 2,780 r. Microscopically the epidermal cells showed only occasional swollen nuclei up to 1,390 r, with more marked changes at 2,780 r.

For therapeutic purposes Ebbehøj ¶ recommends that the radiation used for treating skin lesions be chosen with a skin H. V. L. equal to the thickness of the diseased part or two-thirds of this thickness. These recommendations are based on his work in treating skin cancers. The clinical observations in the treatment of skin cancers are of particular interest because of the ability to assess clearly the results of therapy by the presence or absence of the disease during a five-year period of observation. Ebbehøj found only two recurrences among 93 patients treated and the recurrences were local in the previously involved site. Mosekilde [20] also

¶ References 4 and 5.

reported on the results of 603 cases of skin cancer treated with radiation with a H. V. L. of 1.6 mm. of skin. He found 4,200 r as effective as 5,100 r. In this large series 90.4% were cured in five years, and when the recurrences were treated, the total cure rate was 97%. It should be pointed out that both of these authors curetted the lesions before the radiation therapy if they suspected them of being more than 1.0 mm. thick.

The unit chiefly employed in the treatment of this series of cases was that manufactured by the International X-Ray Corporation. The tube was a standard Machlett beryllium-window tube. In the light of our experience during the past two years, it seems highly probable that in the early phases of this study the delivery of very soft x-rays from the tube varied considerably more than might be regarded as desirable, because of inadequate voltage stabilization, a timer which was not adequate for very short exposure, and the general technical difficulties of calibration. During the last two years of our experience, it is believed that the amount of x-rays reaching the skin did not vary much more than 10% of the calculated dose.

The initial unit employed in this study was calibrated by Mr. C. B. Braestrup on Feb. 14, 1947. In common with some other commercial beryllium tube units available at that time, it was of rather ersatz character. The generator was a Pantoderm, and the tube a Machlett AEG-50-81-T with an inherent filtration equivalent to approximately 1.0 mm. of beryllium. At a kilovoltage of approximately 14 and a milliamperage of 15, the unit delivered 100 r of very soft x-rays in 21 seconds at a distance of 20 cm., and the half-value layer was recorded as 0.025 mm. Al. At a kilovoltage of approximately 18, the unit delivered 100 r in 12.4 seconds at a target skin distance of 20 cm., and the half-value layer was recorded as 0.034 mm. Al. During the first two years of use of the unit, rays with a half-value layer of 0.025 mm. Al were used almost routinely. Calibration at a kilovoltage of 9 was given by extrapolation, but, on the advice of the physicist, no treatment at this kilovoltage was attempted, because of the very large errors resulting from changes in the voltage of the primary circuit. In retrospect, it is considered that the doses given during this period at a kilovoltage of approximately 14 may well have varied by 20% or more, because of the absence of an adequate voltage stabilizer.

Because of a number of vexing inadequacies and inconveniences in this unit, it was replaced in March, 1949, by a Model 8A Bucky therapy apparatus manufactured by the International Medical Research Company. This unit had a kilovoltage range of 0 to 50 kv. and the radiation was delivered by a Machlett tube AE6-50 with an inherent filtration equivalent to approximately 1 mm. of beryllium. This unit was calibrated in March, 1949, by Mr. C. B. Braestrup and in June, 1949, by Dr. S. Reid Warren Jr. The output of roentgens per minute at a distance of 10 cm. was calculated as 1,670 by Mr. Braestrup and as 1,520 by Dr. Warren, at a kilovoltage of 15. The half-value layer at this kilovoltage was rated as 0.038 mm. Al by Mr. Braestrup, and 0.045 mm. Al by Dr. Warren. The agreement on output as obtained by these two competent x-ray physicists in the calibrations performed approximately three months apart may be considered good. It is to be noted that the half-value layer at 20 cm. is approximately 0.001 mm. Al higher than at 10 cm. because of slight hardening produced by air filtration. In the light of later calibrations made by Dr. Warren after restandardization of his Victoreen 250-R nylon chamber, it would appear that a half-value layer of 0.034 mm. Al at this kilovoltage

was more nearly correct. Both of these physicists were in agreement that attempts to operate the unit below 10 kv. would be productive of serious errors considerably above the 10% error which might be anticipated at 15 kv.

With the unit installed in March, 1949, a toggle switch permitted a change in kilovoltage from the 0 to 15 kv. range to the 15 to 50 kv. range. A warning that x-rays were being delivered at this higher kilovoltage was given by a buzzer. Our experience, and that of others, has shown that this is a completely inadequate safety device. It should be recalled in this connection that beryllium-window tubes are

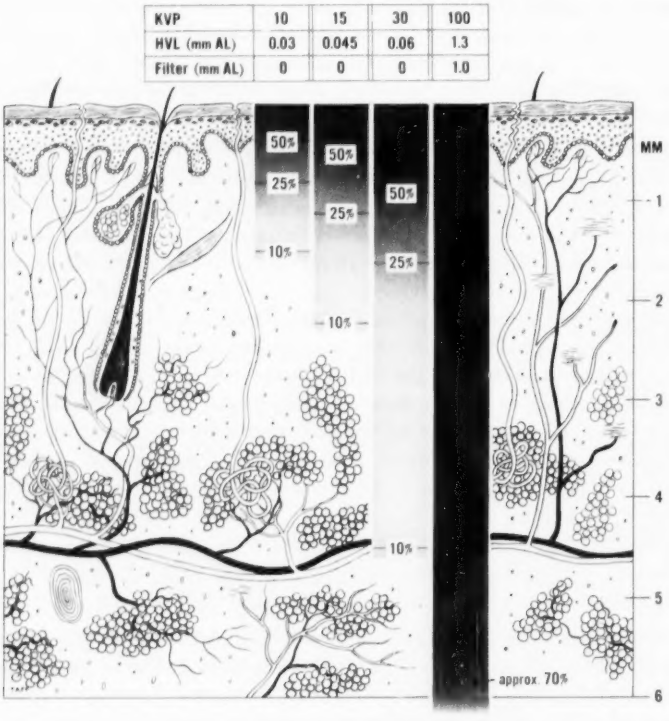

Fig. 6.—Schematic scale representation of penetration of x-rays of varying wave lengths into skin (on basis of preceding summary).

capable of delivering 500,000 or more units per minute at contact distances, at kilovoltages of 45 or more.

The voltmeter scale supplied with this unit did not have adequate spacing to permit easy reading in the lower voltage scale. In July, 1949, therefore, a new double-scale primary kilovolt meter was installed. It was mistakenly not felt necessary to have a recalibration of the unit at that time, since the replacement of a voltmeter would ordinarily mean simply that a duplicate device had been installed. It soon became evident, however, that the biologic effects on the skin of a dose of 150 r, especially in respect to hyperpigmentation, were considerably greater than before the change in the unit. The standard superficial dose for the treatment of

inflammatory processes was therefore reduced from 150 to 75 r. Later recalibration of the unit indicated that the output had been increased by approximately 100%, and the radiological physicist, Dr. S. Reid Warren Jr., gave the following advice to the manufacturer:

(1) That any change in therapy apparatus made by the representative of a manufacturer be reported in detail to the physician who owns the equipment with a request that the calibration be checked immediately, and that receipt of the manufacturer's letter be acknowledged by the physician.

(2) That a copy of the letter from the manufacturer be sent to the physicist who last calibrated the unit, with a note stating the reason for informing the physicist.

With the installation of a voltage stabilizer and continued improvement in the accuracy of the calibration method, this unit has for the past year been operated by us with reasonable confidence that the calculated dose is actually being delivered. It will, it is believed, be found that competent radiological physicists have reached this point of view only recently. It is our own opinion that it is probably highly unsafe to operate beryllium-window tubes routinely with a variation of the kilovoltage from very low to high kv. ranges. We believe that the therapists would be well advised to have two separate units, one to be operated only in low kilovoltage ranges, and the other to be employed for delivering standard superficial therapy.

CLINICAL EXPERIENCES

The individual doses employed for inflammatory processes of the skin and psoriasis varied from 75 to 300 r. In no case did we observe any visible change in the skin lesion or the surrounding normal skin from a dose of 75 r. The effects of doses of 150 r were, as a rule, equivocal. Doses of 300 r frequently showed a more marked therapeutic effect, but in brunette skins often produced a degree of hyperpigmentation sufficient to be objectionable to the patient. This tended to be extremely marked in a few very brunette patients. When doses of 300 r were used, treatments were ordinarily not given more often than every two weeks. The doses employed in a few selected patients with intradermal epithelioma or superficial basal cell epithelioma were, naturally, much higher.

The various types of cases treated may be conveniently divided into (1) several varieties of dermatitis and eczema, (2) anal and vulvar pruritus of varying etiologies, (3) psoriasis, (4) intraepidermal epitheliomas and superficial basal cell epitheliomas, (5) warts of various types, and (6) nevus flammeus. The tabulation of our data on these patients has been extensive, but there is no reason to obscure the main conclusions by a mass of less important or irrelevant details. In general, therefore, we shall confine our statement of results to a summary of the number and types of disease treated, the over-all results in the patients followed for varying periods of time, the results in those patients of whom the observations may be regarded as adequately controlled, and a statement as to undesirable sequelae, if any.

Psoriasis.—Seventy-eight patients with psoriasis received low voltage x-ray therapy (H. V. L. Al 0.025 to 0.034 mm.) in varying amounts, the maximum being a total dose of 7,320 r divided into 34 exposures. One patient received 6,000 r divided into 14 exposures; 2 received between 5,000 and 6,000 r; 3 between 4,000 and 5,000 r; 2 between 3,000 and 4,000 r, and 10 between 2,000 and 3,000 r. The rest received less than a total of 2,000 r to any one site.

Of the entire group, 44 were brought under temporary satisfactory control in respect to the skin lesions, though in no case would we attribute this entirely to low voltage x-ray therapy. Five patients showed no improvement whatever, even temporary. Of the group of 78 patients, the observations in respect to the effect of low voltage x-ray therapy alone were adequately controlled in 10. In these patients certain sites were selected for treatment; other areas were not treated. A competent observer saw the patient before and after such treatment without knowledge as to which areas had been treated. In two of these patients, one receiving a total of 1,000 r and another a total of 3,000 r (in divided doses), no effect from the very soft x-ray therapy could be detected. In the others, varying degrees of greater improvement of the treated as compared with the untreated sites were noted, though this never progressed to complete involution. The results from very soft x-ray therapy were, moreover, generally rather evanescent. In extremely thick lesions, particularly those in the scalp, no improvement was noted.

Conclusion: In the treatment of psoriasis, we are unimpressed with any outstanding regular effectiveness or the degree of permanency of the effects of very soft x-ray therapy. Routine treatment of psoriasis with them is not recommended. An unusual exception may be made in the case of psoriasis of the palms and soles, or prominent lesions on the face, in which every effort toward rapid involution is desired. While no direct comparison of very soft x-ray with standard superficial x-ray therapy was made in the treatment of psoriasis, it is our opinion that the results in lesions which are superficial and not too thick will be fully as good. It is not proposed to use any standard x-ray therapy for comparison, because we have completely discontinued such treatment for psoriasis.

Anogenital Pruritus.—Sixty-four patients with this diagnosis were treated. Some patients had inflammatory changes which might be regarded variously as intertriginous psoriasis, seborrheic dermatitis, or moniliasis; others had no changes aside from those due to excoriation. It was not considered possible to carry out an adequate controlled study of very soft x-ray therapy in any of these patients. In general, the initial concomitant treatment consisted of avoidance of soap and the use of Quotane ([1-β-dimethylaminoethoxy] 3-n-butylisoquinoline monohydrochloride) ointment for antipruritic effect. Twenty of the patients were considered cured sufficiently to be discharged; 33 were significantly improved, and 11 showed no improvement.

The highest total dose of very soft x-ray given was 3,650 r, divided into nine treatments. Three other patients received 3,000 r or more. Eight patients received between 2,000 and 3,000 r; the remainder less than 2,000 r. An occasional patient regularly professed marked relief from itching, usually of temporary nature, after each treatment. This is similar to that experienced with standard superficial x-ray therapy, and is difficult to interpret on any basis other than psychotherapeutic. No direct comparison with standard superficial x-ray therapy was made, but the results with very soft x-ray seem entirely comparable, on the basis of our previous experience.

More recently it has been possible to compare the effectiveness of hydrocortisone ointment, in a strength of 1.0 or 2.5% with very soft x-ray therapy. There is no comparison whatever; hydrocortisone ointment is more regularly and rapidly effective in a much higher percentage of cases. After this considerable experience in

the treatment of anogenital pruritus, it is possible that we shall employ very soft x-rays occasionally in resistant anogenital itching, but certainly not often nor in any long-continued series of exposure.

Circumscribed Neurodermatitis.—Forty-seven patients with this condition were treated. In two of the patients the observations were regarded as fully controlled. In one of these patients no objective change was demonstrated, and in the other there was slight objective improvement confined to the area treated.

In 18 patients the localized neurodermatitis was regarded as temporarily cured following combined therapy with very soft x-rays and local treatment. In 21 patients there was some improvement, and in 8 there was no change whatever. It was quite obvious that in thickened psoriasiform neurodermatitis of the posterior scalp in women, no change occurred from very soft x-rays alone.

In localized neurodermatitis, recent experience with topical hydrocortisone therapy has demonstrated that it is temporarily effective in a high percentage of cases. It is undoubtedly more so than very soft or standard x-ray therapy per se, in our experience, and we would also regard several other methods of topical therapy as superior to any type of x-ray therapy.

Atopic Dermatitis.—Thirty-nine patients with atopic dermatitis received varying amounts of very soft x-rays. The highest total amount given was 3,900 r, and in only one other patient was the total dose above 3,000 r. The number of treatments in all cases varied from 2 to 15. No suggestion of any sequelae from very soft x-ray therapy was noted in any patient.

In three patients, the results of treatment were observed on a controlled basis. All the patients showed slight objective improvement of the treated areas, but the effects were temporary, persisting for not more than a week or two.

It is well known that it is extremely difficult to determine the effectiveness of any particular method of treatment in this disease of erratic and unpredictable course. In our fairly extensive experience in the treatment of atopic dermatitis with very low voltage x-ray therapy, we must conclude that it is a measure which is highly uncertain in its effects, and that improvement is short, if obtained at all. A variety of local treatments are fully as effective, at least temporarily. It is not our intention to treat any further patients with atopic dermatitis by means of very soft x-rays, or any type of radiotherapy for that matter.

Contact-Type Eczematous Dermatitis.—Forty patients with this type of chronic dermatitis were treated. In two of the patients the observations were on a controlled basis; in one of them cure of the treated area resulted, and in the other there was significant objective improvement.

It was extremely difficult to be certain as to whether or not the administration of 150 to 300 r doses of very soft x-rays in this type of dermatitis had any lasting good effect. The effects are certainly not striking or regular. On the basis of our experience it is possible that we shall occasionally administer very soft x-rays to patients with intractable contact-type dermatitis, when other methods of treatment have failed. Wherever possible, it will be our policy to treat only one area of involvement, to determine the advisability of continuance of such therapy.

Seborrheic Dermatitis.—Twenty-two patients with seborrheic dermatitis were treated. In only one of these was the observation of the effect of very soft x-ray therapy strictly controlled, and cure of the treated site resulted after the administra-

tion of 1,200 r in divided doses. In the entire series no very marked change in the course of such patients toward improvement or cure was evident in relation to the administration or lack of administration of very soft x-ray therapy.

From our experience, it would appear that the results of very soft x-ray therapy in seborrheic dermatitis are modest, and this is in accord with our previous experience with standard superficial x-ray therapy. It is not proposed to use the method routinely in the future, and its occasional use will be reserved for patients with intractable seborrheic dermatitis with, wherever possible, an effort to demonstrate definitely whether or not such treatment alone is capable of causing improvement of and by itself.

Eczematous Dermatitis, Unclassified.—Seventy-five patients with chronic eczematous dermatitis of various types were treated with very soft x-rays. In three of the patients the observations were on a controlled basis; in two of these the very soft x-ray therapy seemed definitely to contribute toward cure of the condition, and in the other there was slight objective improvement as compared to untreated sites.

The doses administered varied from 75 to 300 r per treatment, and the total dosage was generally low for this type of therapy, one patient receiving slightly over 4,000 r and another 3,600 r. The rest of the patients were given a total of 2,000 r or under.

In this type of dermatitis, our conclusions are entirely similar to those arrived at in the case of eczematous contact-type dermatitis.

Epitheliomas.—Seven patients with one to numerous superficial basal cell epitheliomas were selected for treatment with very soft x-rays. No patients with squamous cell epithelioma were treated, nor did we consider doing so. A dominant consideration in selecting these patients was whether or not they would be available for prolonged follow-up examinations of the sites treated.

F. E. J., a woman, aged 68. This patient had had psoriasis of minimal severity and extent since childhood. She had been given a fairly prolonged course of treatment with arsenic by mouth at age 21. For the past 10 years, or possibly more, she had been developing scattered epitheliomas of the trunk and scalp. The lesions of the scalp were in general thick and rather exuberant; those on the trunk were superficial and showed a morpheiform type of scarring at the center. A number of lesions had been treated elsewhere with "standard" x-ray, with atrophic sequelae and tendency to ulceration. Twelve superficial basal cell epitheliomas were treated in this patient between May, 1950, and July, 1952. The total amount administered was between 2,500 and 3,000 r, treatments variously being given in two exposures, one of 1,500 r and one of 1,000 r, or two treatments of 1,500 r each, or five to six treatments of 500 r each. Exposures of the order of 1,500 r produced a sharp local reaction and epithelitis, with an apparent marked specific effect upon the tumor tissue. In all instances the tumors disappeared completely, and in only one lesion was there any evidence of atrophic sequelae, that of a lesion which had received a total of 2,784 r. The follow-up of this patient is obviously incomplete, but the results of therapy to date have been extremely satisfactory. During the period of observation, two thick epitheliomas of the scalp were removed by surgical excision.

R. K., aged 33, was previously treated for acne of upper trunk, for which an unknown amount of x-ray therapy had been given. The patient presented multiple papular to small plaque-type lesions, morphologically typical of superficial epithelioma. Biopsy confirmed this diagnosis. Six epitheliomas were treated with a single dose of 3,730 r of very soft x-ray therapy (H. V. L. 0.034 mm. Al). A sharp epithelitis was noted at all these sites. The superficial tumors disappeared, but all sites present definite superficial atrophy two years later (Fig. 7). These lesions are not bothersome except for extreme sensitivity to sunlight. Surgical excision of them probably will be undertaken.

Four other lesions of similar nature were treated with a single exposure of 2,238 r of very soft x-rays. All of these lesions disappeared completely without any residual sequelae, and there is no evidence of recurrence two years after treatment.

In this patient there appeared to be a point between a single dose of 2,200 and 3,700 r at which a reaction sufficient to produce superficial x-ray sequelae was produced. It is considered from this experience that the individual doses given to this patient were excessive, and that, as with standard superficial therapy, division of the total dose is advisable.

J. L. O., a man, aged 57. This fair-skinned Irishman presented a considerable number of lesions of wide variety on the face, trunk, and extremities. Biopsies revealed, variously, multiple superficial epitheliomas, senile keratoses, seborrheic verrucae, and one lesion which proved to be a small squamous cell carcinoma. The senile keratoses were treated by electrocoagulation and curettage, with satisfactory results. Following excision biopsy, the site of the squamous cell carcinoma was given standard x-ray therapy in divided doses, to a total of 5,000 r. Twelve superficial epitheliomas have been treated with very soft x-ray in this patient, in total doses

Fig. 7.—Atrophy one year after single exposure of 3,720 r of very soft x-ray (H. V. L. 0.034 mm. Al) in treatment of superficial basal cell epithelioma.

varying from 2,500 to 3,000 r divided into two or three exposures. Moderate epithelitis was noted at all sites of treatment. All gross evidence of tumor tissue has disappeared, and it is impossible to locate the original sites of the lesions on inspection; there are no sequelae whatever. The period of follow-up since the original treatment in four of the lesions has been four years.

J. M., aged 77, a white woman. This patient, a Christian Scientist, had undergone successful resection of a carcinoma of the colon four years previously. She presented a superficial epithelioma of the right hip, measuring 5 by 4.2 cm., which had been gradually extending in size for at least 20 years. There had been some increased extension in the past two years. The lesion was treated initially in successive exposures of 1,000 r each at intervals of two weeks to a total of 4,100 r. The lesion disappeared entirely with the exception of a small area at the lower portion. Incomplete involution and some extension of the lesion occurred at the lower portion, and 5,000 r more were given to a target 2.5 cm. in diameter, in four divided doses. In view of the patient's age, it is unlikely that follow-up to determine the permanence of cure will be possible. There can be no question, however, that very satisfactory involution of a large long-standing superficial

epithelioma was achieved much more easily and with less sequelae than would have been the case with surgical excision and grafting, with standard x-ray therapy, or with electrocoagulation and curettage.

J. C. L., aged 74, presented numerous epitheliomatous and preepitheliomatous lesions of the arms and trunk, which had been appearing steadily for some 25 years. A number of sites had previously been treated with standard x-ray therapy, with unsatisfactory results in respect to atrophy, necessitating later excision of two of the areas. Two epitheliomas so treated had relapsed. In general, the lesions were considered too thick for very soft x-rays, of the type being routinely administered, and were variously treated by surgical excision in the case of larger lesions, and thorough electrocoagulation and curettage in the case of smaller ones. In a four-year period of observation, no recurrence has been noted in the 30 lesions so treated. A single lesion approximately 2 mm. thick was selected for treatment with very soft x-rays. An initial

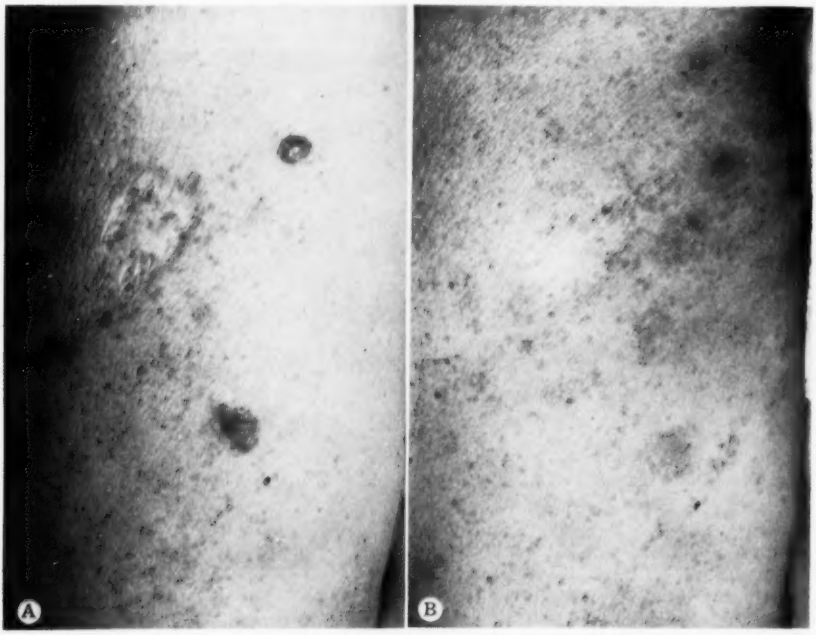

Fig. 8.—*A*, nodules of leukemia cutis in patient with no general hematologic evidence of leukemia. *B*, appearance two months after administration of two doses of 500 r each of very soft x-rays (H. V. L. 0.034 mm. Al). Some 20 lesions have been similarly treated with, to date, invariable complete disappearance of the individual nodule.

dose of 1,000 r was given through a 2 cm. port. The patient was not seen until some months later, at which time the epithelioma had completely disappeared, without any visible sequelae whatever. The period of observation of this lesion after treatment has been only one year.

S. N. M., a white woman, aged 83. This patient has been seen at intervals over a period of 14 years for various dermatologic lesions, principally keratoses and papillomas. In 1948 a superficial epithelioma, 7 mm. in diameter, was noted in the right anterior axillary fold. The patient stated that it had been present for some three years. The patient's general health was somewhat precarious, and it was not considered necessary or advisable to excise the lesion surgically. It was examined on four occasions subsequently, and in March, 1950, had increased to a diameter of 1.3 cm. The patient was concerned about it. A single exposure of 2,000 r of very soft x-rays was administered through a 2-cm. port. Moderate epithelitis was noted, with

an almost liquefying reaction in the tumor tissue. There was some evidence of pigmentation in May of 1950, but no evidence of tumor. Subsequent examinations were made in June, 1951, October, 1952, and May, 1953. After this period of over 3 years, there had been no evidence of recurrence. On examination with a lens, barely perceptible superficial atrophy was visible.

Summary: On the basis of this experience with 43 superficial basal cell epitheliomas treated in seven patients, the results may be regarded as highly satisfactory. In no patient has the epithelioma failed to disappear, and there has been no evidence of recurrence of any of the lesions except one during periods of observation varying from one to four years. In one patient, R. K., the results in respect to atrophic changes are unsatisfactory, though by no means serious, and grossly of a much more superficial character than is ordinarily noted after standard x-ray therapy.

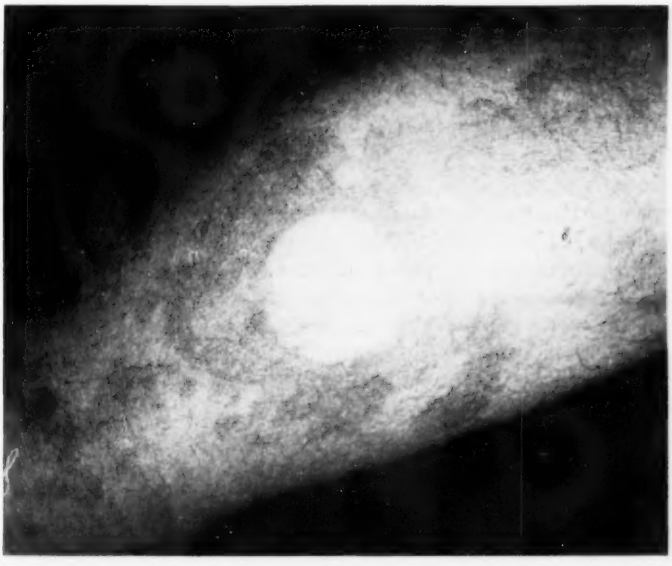

Fig. 9.—Apparent blanching effect on nevus flammeus four weeks after administration of 450 r of very soft x-rays (H. V. L. 0.035 mm. Al). This effect is not maintained, however, and the appearance is probably in large part due to hyperkeratinization from mild epithelitis, and not to the effects on dilated blood vessels.

It is to be emphasized that these results were obtained in superficial epitheliomas, the thickness of which was certainly not over 2 mm. For thicker lesions, x-rays of a character to produce a suitable half-value tissue dose would have to be carefully selected. Such selection should, in our opinion, be made by a physician of great competence in radiologic physics and in the selection of proper depth doses, and not by individuals who simply possess a beryllium-window x-ray unit and have occasion to treat such lesions relatively infrequently.

On the basis of this limited experience we are, however, convinced of the validity of the principle of selecting x-rays of wave length suitable to the thickness of the lesion to be treated, both from the standpoint of cure of the tumor and of reduction

of chronic progressive sequelae at the site of treatment to a minimum. The doses employed in this series of patients were tentative, and are probably less than optimum.

Nevus Flammeus.—Twenty-three patients with port-wine angiomas of varying extent have been treated. The total doses employed have varied from 600 to 16,000 r. One patient received a total of 16,000 r; two patients, between 7,000 and 8,000 r; one patient, 6,000 to 7,000 r; four patients, 5,000 to 6,000 r; two patients, 4,000 to 5,000 r; three patients, 3,000 to 4,000 r; five patients, 2,000 to 3,000 r; four patients, 1,000 to 2,000 r, and one patient, 600 r. The individual treatments varied from 300 to 600 r, and were administered at intervals of three to five weeks as a rule. A dose of 600 r may produce a degree of immediate reaction which is worrisome, and individual doses under 500 r are preferable, if the treatment is used at all. No evidence whatever of sequelae has been noted to date.

Results: In three patients, observations of the effect of 500 to 1,000 r to a portion of the lesion were made before treatment of the entire lesion was attempted. In each of these instances, slight to moderate blanching of the treated area was noted, though this may be more apparent than real by reason of the slight hyperkeratosis which may follow such an exposure and which may simply obscure the underlying vascular portion slightly.

The results, on the whole, have been disappointing in regard to significant improvement of the cosmetic appearance. In only one patient was the result of a degree to make the lesion unnoticeable on casual observation. In this patient, in whom the lesion was on the forehead, no make-up is required, and the appearance of the skin is entirely presentable. In six patients who received total doses of 1,800 to 5,480 r, there was no detectable change whatever. In nine patients there was agreement that slight blanching had occurred, but it was very difficult to demonstrate this photographically. The patients still required heavy make-up to obscure the lesion if it was on an exposed site. In seven patients the degree of improvement was sufficient so that ordinary light make-up obscured it satisfactorily.

In only one patient was the dose carried to a very high total, of the order which has been used with grenz rays of indefinite quality in the past. This patient was seen on two occasions with Dr. Gustav Bucky. We are still concerned as to possible eventual sequelae in this patient, though the area is one susceptible of excision if necessary.

Conclusion: The results in the treatment of nevus flammeus, in the doses employed, have not been sufficiently encouraging to make us believe that the method has distinct value. It is possible that the improvement noted in some patients would have occurred spontaneously, though we somewhat doubt this. The method of treatment is not difficult in older children, but is decidedly tedious in young children and infants. It is unlikely that we shall undertake the treatment of any considerable number of patients with nevus flammeus by this method in the future. If it is undertaken, however, it is believed advisable in the case of larger lesions to treat only a portion of the lesion initially, to determine as accurately as possible whether or not the vascular changes are "radiosensitive."

Sequelae.—A careful examination of all patients has been carried out for possible sequelae from low-voltage x-ray therapy, for as long as has been possible. These follow-up examinations are being continued. No permanent changes of any type

have been noted in any patient to whom doses of 150 to 300 r were given not less frequently than every week, or in patients to whom doses of 300 to 500 r were given at intervals of three to four weeks. Continued follow-up of all patients who have received more than a total of 2,000 r will be attempted during the next decade.

The table gives data on patients receiving over 4,000 r in divided doses, with the diagnosis and period of follow-up observations:

No visible sequelae have been noted at any of the treated sites in the above patients.

A total of 109 patients in this series received very soft x-rays in divided doses to a total of over 2,000 r. Of these, 55 have been observed for a total of over two

Patients Who Received More than 4,000 r in Divided Doses

Total Dose	No. Exposures	Diagnosis	Duration of Follow-Up Since Treatment, Mo.
16,000 r *	25	Nevus flammeus	26
7,320 r	34	Psoriasis	45
7,250 r	13	Nevus flammeus	11
7,120 r	24	Nevus flammeus	20
6,360 r	18	Nevus flammeus	56
6,000 r	14	Psoriasis	9
5,480 r	14	Nevus flammeus	13
5,460 r	17	Nevus flammeus	54
5,370 r	19	Psoriasis	42
5,262 r	25	Psoriasis	23
5,000 r	14	Nevus flammeus	47
5,000 r	15	Nevus flammeus	41
4,950 r	14	Psoriasis	30
4,800 r	8	Nevus flammeus	9
4,600 r	9	Darier's disease	11
4,530 r	27	Psoriasis	22
4,280 r	28	Dermatitis of hands	21
4,500 r	8	Small hemangioma	14
4,200 r	5	Small hemangioma	11
4,190 r	17	Localized neurodermatitis	37
4,070 r	31	Otitis externa	39
4,200 r	9	Nevus flammeus	10
4,190 r	17	Psoriasis	37
4,200 r	9	Nevus flammeus	10

* Treated on advice of Dr. Gustav Bucky.

years after treatment. No sequelae have been noted. (None of the patients treated for epithelioma are included in this group.)

COMMENT AND SUMMARY

In reviewing the clinical literature in respect to grenz ray therapy, and more particularly from discussions of this method of treatment by clinicians, one is struck with the wide diversity of opinions expressed. It is possible that some of this disagreement may be due to the fact that therapists have at times attempted to compare results obtained by treatment with soft x-rays of considerably different character. It also seems probable that in some reports the effect or lack of effect of treatment may have been more representative of natural variations in the course of the diseases treated than of any influence exerted by therapy.

There is also considerable controversy at the present time about the advisability of standard superficial x-ray therapy for any type of benign skin disease. Here again, though accurate calibration of standard superficial therapy units has been practicable since 1925-1930, the evidence is still not completely convincing as to the effectiveness of such therapy in a considerable number of skin diseases for which it has been advised, especially if one considers long-term results rather than evanescent ones. The number of studies of standard x-ray therapy in which there has been some attempt at controlled observations is extraordinarily few. In a recent study by Crissey and Shelley,[21] however, it was shown beyond doubt that standard x-ray therapy, in which the treatment was administered to portions of lesions, produced a consistent effect in lichen simplex chronicus, lichen planus, and psoriasis, and very slight effects in nummular eczema, contact dermatitis, and acne vulgaris. The authors expressed doubt that the use of x-rays in the last three conditions are justified. Particularly in contact dermatitis, they agree with the statement of MacKee and Cipollaro [22] that x-rays are not indicated in a majority of cases of dermatitis venenata. In the study by Crissey and Shelley, the eventual outcome of treatment was not determined for longer than 16 weeks; the study was designed simply to determine the immediate effects.

In a later report, Hurley and Shelley [23] record the induction of a delayed Koebner phenomenon in one of the patients with psoriasis treated by Crissey and Shelley. The observation in this patient was remarkable in that the appearance of the psoriatic lesion sharply limited to the previously irradiated skin did not occur until 18 months after the therapy was given. There was no recurrence in the surrounding skin which had received no therapy.

In spite of demonstrations of some temporary effect of x-ray therapy in certain benign dermatoses, the justification for such therapy must rest on the eventual result, particularly in terms of harm produced. Current consultative experience of dermatologists, radiologists, and surgeons includes a large number of disheartening instances of late x-ray damage to the skin, almost entirely in patients treated over 20 years ago by physicians of varying competence. Such cases are common, and the observation of them is a shocking experience which inevitably produces a profound prejudice against the use of a potentially dangerous method of treatment for a benign dermatosis. As a result, it is our current practice almost never to employ "standard" superficial x-ray therapy in a chronic benign dermatosis. Epilation in chronic tinea capitis in children is an exception.

Our experience in the treatment of 550 patients with very soft x-rays having a half-value layer of from 0.025 to 0.035 mm. of aluminum may be summarized briefly as follows:

1. *Radiophysical Considerations.*—It is of the utmost importance that any therapist who proposes to administer very soft x-rays have knowledge of the important radiophysical considerations, and of the several means by which errors in dosage may occur. The most important of these are (1) the lack of an efficient voltage-regulating mechanism, with resultant marked variation in output resulting from small variations of kilovoltage; (2) difficulties in the measurement of very soft x-rays, the methods for such measurement having reached a phase of general practical value and accuracy only recently; and (3) the inadequacies and structural defects of some therapy units in current use, particularly in respect to preventing the delivery of x-rays at higher kilovoltages without the insertion of a filter. It is

our own conclusion, after a series of somewhat discouraging experiences, that the calibrations in the hands of a competent radiophysicist with special experience in the measurement of soft x-rays may now be regarded with confidence. In the use of very soft x-rays we prefer to employ a special unit, in which there is no possibility of a delivery of x-rays at a kilovoltage higher than 15. Nevertheless, it is possible that some available units with a wider kv. range overcome this objection. The prevention of delivery of x-rays at higher kilovoltages must be absolute; it is completely unsafe, in our opinion, to depend upon toggle switches, warning lights on the control board, buzzers, double-scale voltmeters, etc.; errors have resulted from all these.

2. *Individual Dosage and Effects Produced.*—With x-rays having a half-value layer of 0.25 to 0.035 mm. Al, we have never observed any effects whatever from doses of 75 to 100 r; it is believed that the individual dose on any inflammatory process should be at least 150 r. It is our current practice, ordinarily, to administer 300 r. We have never observed significant erythema from such a dose, though in brunette patients the amount of pigmentation produced may be significant and annoying. A dose of 500 r, particularly if given through a large port, may produce definite erythema and occasional mild epithelitis. This effect is increased at 1,000 r, and doses of 1,500 r on "thin skin" will regularly produce a sharp erythema and some swelling of the skin, which slowly subsides with some scaling. We have administered doses of this magnitude, however, only in superficial epitheliomas.

The sole instance of significant x-ray atrophy which we have encountered was in a patient in whom a number of superficial epitheliomas received a single dose of 3,720 r. It would appear, therefore, that the single dose of such therapy which will produce late atrophic changes lies somewhere between 1,500 and 3,720 r, though it is of course possible that late changes may be noted with the passage of a period of time longer than this study.

3. *Total Divided Dose Tolerated.*—It will be noted that 24 patients who have received between 4,000 and 16,000 r individual doses have been followed for periods of 9 to 56 months, and in none of these have any sequelae whatever been noted. With the exception of the patient who received 16,000 r, the total dose used may be regarded as conservative. Continuing follow-up of such patients will be maintained, but we have reasonable confidence that no untoward changes will be noted in the future.

4. *Clinical Effects.*—The only condition treated in which a regular good effect of treatment was encountered has been superficial epitheliomas. These effects were produced by total amounts of irradiation which are surprisingly small in some instances, and such doses are by no means represented as being optimal. The results of treatment of 43 very superficial thin basal cell epitheliomas in seven patients were highly satisfactory, however, and in only one patient were significant atrophic effects produced. It will be noted, however, that the longest period of observation in these patients is four years; but in this type of lesion, recurrence ordinarily becomes evident long before this. In particular, we would emphasize that this experience is not to be interpreted as an indication for the treatment of thicker basal cell epitheliomas or of epitheliomas of a higher degree of malignancy. We do believe, however, that this is evidence of the usefulness of selecting a proper depth dose for such lesions.

In some patients with various benign conditions of the skin, including particularly various types of dermatitis and eczema, anal and vulvar pruritus, and psoriasis,

occasional transitory good effects of treatment were demonstrable, on a controlled basis. However, these effects were by no means regularly demonstrable, and were often very transitory. We do not believe that the effectiveness of such therapy is sufficient to justify its routine use. It is possible that we may employ very soft x-rays in the treatment of these conditions when they prove resistant to other methods of therapy, but it is not anticipated that the indications for this will be frequent. It is, moreover, planned to continue the custom, whenever possible, of treating only one lesion or a portion of a large lesion initially, to determine whether or not such therapy is of real value in the particular patient being treated.

The results in the treatment of port-wine stains with very soft x-rays have, on the whole, been disappointing. With the exception of one patient who received 16,000 r, the total dose of very soft x-rays used in our patients will be regarded by some as inadequate. We have been unwilling to exceed total dosages in the neighborhood of 5,000 r, however, because of uncertainties as to the possible eventual sequelae. Even with these dosages, the treatments are tedious and long drawn out, since it is inadvisable to give individual doses larger than 400 and 500 r, and treatment should not be given oftener than every three to five weeks.

ABSTRACT OF DISCUSSION

Dr. Frank C. Combes, New York: I have enjoyed and profited very much from Dr. Pillsbury's talk. He has given us his experience with this controversial method of radiation therapy in diseases of the skin. For the last eight years, I have used this method, with both water-cooled and air-cooled Machlett tubes, with beryllium windows, and I agree with Dr. Pillsbury that the limitations of the grenz-ray range in terms of half-value layers is rather a matter of opinion and should not be arbitrarily designated.

However, in view of the great differences in energy output, involving variations, as he has shown, of only 1 or 2 kv. in this range, certainly some kind of limitation is indicated, and particularly since in the literature you will read many references to so-called grenz rays produced by potentials of from 20 to 40 kv. Naturally, this is not in the grenz ray range.

Otto Glasser has designated the so-called grenz ray range in half-value layers as between 11 and 33.5 μ of aluminum. Certainly, in using values of 34 μ—I think that is what Dr. Pillsbury mentioned—he still is for general purposes in the grenz-ray range.

Poor results in therapy are, in almost all instances, as he has mentioned, due to improper calibration, and satisfactory calibration was not possible until about a year and a half ago, when the Bureau of Standards became capable of standardizing the nylon chamber for "r" unit measurements at short distances and low H. V. L.

It is immaterial whether we refer to this type of radiation as the Bucky rays, supersoft x-rays, or whatever you wish to call them. Certainly, when we speak of any type of radiation, we should not continue to refer to dosages simply in roentgen units or in kilovolts, as Dr. Pillsbury has mentioned. We should always include mention of the half-value layer or quality of radiation.

The very concept of x-ray therapy can readily be paraphrased in an expression of penetrating power, as Dr. Pillsbury has mentioned; and this, in turn, means depth dosage. The principle involved is both simple and direct. We wish to deliver the optimum dosage to the lesion, with minimal damage to structures, either more superficial or deeper; in other words, with radiation of this quality, we are selecting ionizing energy more specifically appropriate to the disease being treated. There are many dermatoses in which grenz rays, I think, are definitely superior to radiation of greater half value layer.

Dr. Pillsbury's experience in the treatment of nevus flammeus has been somewhat like mine. I have recently got fading of lesions, but I have been very hesitant, and I have not got the complete disappearance, although I did see one instance in which a patient received a total of 27,000 r (H. V. L. 0.026 mm. Al), over a period of 20 years for a nevus flammeus in the bearded

region of the face, and there is presently no evidence of the lesion. I saw a photograph of the untreated lesion. There is no evidence now of the lesion, no sign of atrophy, and no sign of any alopecia. The accuracy of the dosage in this case may be open to question.

I think that grenz ray is of great value in the treatment of leukoplakia. It is indicated, certainly, in all the superficial epitheliomata, and is of value also in recurrent contact dermatitis. I think that my results in psoriasis are far better than those of Dr. Pillsbury, and I think that if he removes the scale first and then treats the patient with a lower half-value layer, his results will be better. The scale certainly absorbs to a large extent much of this soft type of radiation.

Basal cell epithelioma, the ordinary type, certainly should not be treated with grenz radiation or any radiation in this range. It is possible, in using half value layers from 40 to 45 μ and giving intensive dosages, preferably fractionated up to around 25,000 or 30,000 r, to get very good results. But I do not treat it with this type of radiation, anyway.

Grenz rays should not be applied to any skin which has received tolerance doses of conventional x-radiation.

In conclusion, I wish to warn those who are unacquainted with this type of radiation that the slightest variation in kilovoltage, in distance, or in time, may result in much greater dosage variation than in superficial radiation given by kilovoltages from 70, 80, 90, and 100. All the customary sequelae which follow this type of conventional radiation dosage will follow the treatment of patients with high therapeutic dosages of grenz ray, except in cases of epithelioma, alopecia, keratosis, and ulceration. Atrophy, telangiectasia, and pigmentation may be produced.

One objection to grenz radiation is the temporary pigmentation which will follow dosages of around 300 to 400 r, with almost any half-value layer in the range. It may last for several weeks and sometimes months.

In addition, I should advise against attempts to calibrate the conventional x-ray machines down to the grenz-ray range, and I doubt whether it is possible to do so. I have always advised against combination machines and machines operated without stabilizers or some source of constant electric potential. There are several unsolved problems with grenz rays, and there is a big field for investigation. A few of these problems are evaluation of the dangers; the accumulation of dosage, which some deny exists, or which they say exists with some modification; the toleration of different skins; variations in intensity of radiation at various sites on the field of exposure; dosage intervals; and systemic effects, which do occur. There are hormonal effects and metabolic effects, which have been reported and certainly do exist, for sometimes upsets in menstrual cycles will occur when large areas of skin are exposed.

DR. MARION B. SULZBERGER, New York: After listening to Dr. Pillsbury and to Dr. Combes, there remains but little that anyone can add to this presentation and discussion.

First of all, I should like emphatically to second what Dr. Combes has just said. Here is a method which, in its proper place and administered in proper fashion, is of value, but for some reason or other, it has fallen into bad odor and disrepute—if not disrepute, at least into disuse. That, I think, has deprived dermatologists of a valuable therapeutic arm and deprived patients with certain types of skin diseases of a valuable form of therapy.

Since 1947, we have been using so-called grenz rays systematically at the New York Skin and Cancer Unit and in my private practice. And they have been studied by our staff also at Bellevue Hospital since long before that time, as Dr. Combes has just told you. In my private practice I started in just as Hanfling and Distelheim did at Bellevue Hospital with paired symmetrical comparisons of the effectiveness of grenz rays (given for the skin affections I shall list and in the dosage which I shall describe to you in a moment) and conventional x-rays (given to contralateral affected sites). In many instances there was no difference in effectiveness; in certain instances there was superiority of effect at the grenz-ray-treated site; and in many instances superiority at the x-ray treated site. By and large, our results could be described as somewhere between those which Dr. Combes has recorded and those which Dr. Pillsbury has described.

I would like to emphasize one thing a little more strongly, perhaps, than did Dr. Pillsbury and Dr. Combes. When one considers the former great inaccuracies of calibration and dosimetry, the former great variability and inadequacies of equipment, and the former great differences in dosage schedules adopted by different men and resulting from different philosophies of treatment, and when one contemplates the former differences in accuracy of recording, one must

realize that this method has, fortunately, tremendous factors of safety. Despite what must often have been huge total doses in the last 20 years, there is no recorded case of a cancer or an ulcer proved due to grenz rays.

You have heard, but it is worth emphasizing once again, that the sequelae which have been seen, while they may be disagreeable, if they occur on a presenting part of a young lady, are of the types that are not particularly disagreeable when they appear on a covered part of an old man, for example—and which are certainly not dangerous. In other words, the dangerous sequelae are really practically nonexistent, even with this tremendous variation and the many errors of dosage and measurement which must have occurred in the past. I have no hesitancy in saying that the record indicates that this range of low-voltage x-ray classes as one of the safest measures when applied by the conscientious trained dermatologist. This is one of the forms of treatment which enables the physician to sleep better. I have practically no worries about sequelae from so-called grenz rays, using them the way we do, with all the factors of safety that we now possess.

I should like to describe to you the dosage schedule which we have made standard in the treatment of pruritus anogenitalis, and in certain cases of psoriasis and of superficial dermatoses of the scrotal region, eyelid and scalp areas, etc., not because it is necessarily the best but because it is one which we think lies well within the zone of safety, perhaps many hundred per cent below the level of danger. We give 200 r for treatment as a standard dose for superficial inflammatory dermatoses, pruritus, etc., generally with a half-value layer a little less than that which Dr. Pillsbury has described, namely 0.028 mm. of aluminum. We repeat these 200 r once weekly for a total of four applications—for a series total, therefore, of 800 r.

Dr. Victor H. Witten and I have set up as a permissible total dose on areas not previously damaged or treated by x-ray, the application of such a series twice per year, that is, once every six months. I think that that is well within the limits of any possible risk of damage. There is quite apparently no danger in that schedule of dosage, judging from what we have seen since Bucky introduced this quality of rays in Europe, judging by the dosages which other people have used with impunity, and now judging by six years of our own experience. (The latter alone would of course, have still been somewhat too short for a final pronouncement.)

I think that here is a modality which requires a presentation and discussion of this kind in order to bring it back into the fold of fullest usefulness in qualified hands.

Dr. Clarence S. Livingood, Detroit: I have not read Dr. Pillsbury's paper, but I did have an opportunity to discuss it with him prior to this presentation.

It seems quite obvious that he has presented a very careful and also an unbiased analysis of this controversial subject. Evidently Dr. Pillsbury and his co-workers were not able to demonstrate a consistent superior therapeutic effect with this modality. As I interpret their findings, grenz-ray therapy is not recommended for the routine treatment of inflammatory dermatoses, such as contact dermatitis and eczematous eruptions. Also, their results seem to indicate that it has only a very limited place in the management of psoriasis. The report of Dr. Pillsbury and his co-workers is a most conservative one and not as enthusiastic as might be interpreted by the remarks of Drs. Sulzberger and Combes.

Finally, I would like to point out that there has been a tendency on the part of some observers (particularly certain manufacturers of this type of apparatus) to adopt a point of view that this is a therapeutic modality with a very wide margin of safety. Physicians have been assured that the use of this type of therapy (in contrast to conventional superficial x-ray) does not involve special training in dermatology or x-ray therapy. It is obvious that this policy is fallacious. It should be emphasized that low-voltage x-ray therapy should be prescribed and administered only by those physicians who have had special training in dermatology; indeed, when on considers all aspects of the matter, it would seem that this policy is just as important as it is in the case of superficial x-ray therapy.

I wish to thank Dr. Pillsbury and his co-workers for this excellent paper. The collection of their data involved a tremendous amount of work, and all of us are grateful for the opportunity to take advantage of their wide experience in this field.

Dr. George C. Andrews, New York: I want to congratulate Dr. Pillsbury on the conservative way in which he talked about these radiations; Dr. Sulzberger's remarks also were

apropos. I think his dosage is very conservative. Of course, you notice that both Dr. Sulzberger and Dr. Pillsbury used dosages of 200 or 500 r, which is in the range of an erythema dose, for each exposure.

Back in 1922, when Bucky brought out this apparatus and when he and Martinstein defined Bucky rays as x-rays produced at kilovolts of 10 to 12 kv., having a half-value layer of 0.02 to 0.03 mm. of aluminum, I got one of his machines; his physicist calibrated it for me, and I used it for many years. Since 1946 or 1947, we have had one of the Machlett beryllium-window tubes and run it at 12 and 25 kv., producing radiations similar to those described by Dr. Pillsbury. We have also used the Phillips contact machine, which runs at 45 kv., and produces radiation of a half-value layer of 0.3 mm. Al.

I agree on the clinical results. They are good on superficial epitheliomas and on superficial angiomas, but on port-wine mark, only once in a great while do we get improvement—which is no better than one gets from thorium X.

Well, the results are all right in a few diseases. It is just a question of how important this type of radiation is. I personally have not found it so very useful. We use it occasionally. We use it on certain superficial lesions. But it is nowhere near as effective as the orthodox x-ray treatment.

Some years ago, as you know, Braestrup and I made a study and we found that radiation produced at 60 kv., half-value layer of 0.07 mm. gave us the best distribution of dosage in the first centimeter of tissue. Now, it is all a question of where you want the radiation; how deep the pathology is. If the pathology is very superficial, you don't need dosage in the first centimeter of tissue. As Dr. Pillsbury said, you may need dosage in the first 3 mm. of tissue. Well, you can't have a different technique for each millimeter depth without utter confusion.

In the early days of radium therapy, we used to use a 0.1 mm. aluminum filter, a 1 mm. aluminum filter, a 0.5 and a 1 mm. silver filter, 0.3 and 0.5 mm. of platinum, and 0.5, 1 and 2 mm. of lead, and the same of brass. We had all those different filters, and one would use one or another, but, finally, after 25 years, everybody is using 0.5 mm. of platinum, and the others have been pretty well forgotten; that is the situation with this type of grenz or low-voltage radiation. It has value, but whether it has enough value in a busy office to give the space for a machine of this type is another matter.

I personally think that with thorium X, you can get most of the results you get with these low-voltage roentgen rays without taking up the room for special apparatus.

Dr. Maximilian E. Obermayer, Los Angeles: One of the discussers has voiced an opinion with which I cannot agree at all; that is, the statement of Dr. Sulzberger that a physician who uses grenz-ray equipment may be able to sleep well. I feel that exactly the opposite is the case.

I was particularly interested in this paper because of the malpractice angle involved, in view of the fact that California exceeds all other states in lawsuits of this nature. Physicians who use roentgen therapy have, indeed, been singled out for such attacks. Therefore, to use an apparatus that cannot be reliably calibrated practically amounts to an invitation to medicolegal difficulties.

The physicist who calibrates most of the x-ray equipment in southern California has recognized this danger and has therefore refused to calibrate grenz-ray equipment, much to the chagrin of the distributor. His stand was endorsed by a prominent medicolegal expert in southern California. This physicist has pointed out that the curve of ion chamber reading, called the constant potential, as was pointed out by Dr. Pillsbury and Dr. Combes, is useful only for the range from 30 kv. upwards. At 10 kv., this curve is practically vertical. This means that a minimal difference in kilovoltage produces an enormous variation in the correction factor, and, hence, in the recorded output of roentgens per minute.

Therefore, until the technical difficulties of measurement are obviated, it would be unwise for any of us to use grenz ray equipment in the state of California.

Dr. Anthony C. Cipollaro, New York: I am very much indebted to Dr. Pillsbury for bringing this very interesting subject before this Association.

There is a great deal of confusion about the biophysics of these low-voltage x-rays, although there should not be. These grenz rays are x-rays; they are produced with kilovoltages of 5 to 15; they have an effective wave length of about 2 Angstrom units, and

they have a half-value layer of from 0.02 to 0.05 mm. of Al. It is as simple as that. There is no confusion whatever regarding these radiations in the minds of such biophysicists as Drs. Otto Glasser, Lauriston Taylor, and Edith Quimby. As a matter of fact, I was discussing this with Dr. Otto Glasser just recently, and he said something to the effect that it is silly to think that grenz rays are radiations whose half-value layer is limited to 0.035 mm. of aluminum, and that anything just a little bit above and anything just a little bit below are not grenz rays but something different.

Ionizing radiations, regardless of wave length or how they are produced, have the same biologic effect. I think it is illogical, in our present state of knowledge, to think that by applying grenz rays, let us say to the mid-dorsal region, constipation or migraine headaches can be cured, as has been written time and again. By the same token, I don't think that there is evidence to indicate that grenz rays have hormonal effects or have indirect effects on remote organs, where these radiations cannot reach. I think that the evidence that has been produced to show such effects is open to question. We all agree that such indirect effects have not been obtained with conventional low-voltage x-rays.

Grenz rays are useful for the treatment of some superficial skin diseases, but are useless for deep or thick lesions. I would not think of using grenz rays for any lesion which has a depth greater than 3 mm. Grenz rays are not capable of reaching to the bottom of such lesions as keloids, ordinary basal cell epitheliomas, and the lymphoblastomas. To use grenz rays for the treatment of such lesions is not logical. However, some of the very superficial basal cell epitheliomas can be adequately treated with this type of radiation, and many of the inflammatory dermatoses which do not have a great thickness can also be so treated.

I have used grenz rays continuously in my office since 1928. First, we used the old Lindemann tube, then we employed "sucked-in" window-glass tubes, and now we have beryllium-window tubes. I have had an opportunity personally to work with physical instruments, with physicists, and with patients, and my thinking is not the same as that of those clinicians who have recently been treating some patients with these radiations and who think that grenz rays can be used as a substitute for x-rays. They cannot.

Just consider depth dosage for a moment. Suppose you want to apply a dose of grenz rays to a lesion which has a depth of 3 mm., and you apply to the surface of the skin 100 r, measured in air. By the time these radiations reach to a depth of 3 mm., there are only 3 r left to do the job of 100 r. Well, you know that these 3 r are not going to have any appreciable effect on a pathological cell situated 3 mm. below the surface of the skin. In order to get what we have learned by experience to be an effective therapeutic dose, you will require nearly 100 r down to the 3 mm. level. To do this, it will be necessary to apply to the surface 10,000 r of grenz rays. If an effective dose of 3,000 r is required in treating an epithelioma, even a superficial basal cell epithelioma, then 100,000 r applied to the surface are required so that after absorption a dose of 3,000 r remains to affect the under surface of the lesion.

Well, gentlemen, it is so much easier and so much more certain to use a conventional superficial x-ray therapy apparatus, isn't it, if you are going to use ionizing radiations for the treatment of an epithelioma, and you don't have to have a special computation machine to figure out the dosages. The clinical experiences which we have had with conventional superficial therapy are adequate to guide us and to help us in handling our everyday radiological problems.

The kodachromes of severe radiodermatitis were startling and frightening. The damage was done with a dual-purpose (grenz ray-superficial therapy) apparatus. The dermatologist who used the apparatus gave me a set of pictures. He deserves high praise for bringing to our attention this possible danger of dual-purpose machines. If the advocates of grenz rays are so certain of the superiority of grenz rays, then why is there a necessity for an apparatus which can be converted from a grenz ray machine to an x-ray machine by the flip of a switch? Dual-purpose radiation therapy machines are dangerous unless better indicators and safety devices are used to warn the user. I am so thankful to Dr. Pillsbury for showing these horrible examples of radiodermatitis, because it is going to alert us to use greater caution in purchasing so called foolproof safe radiation therapy machines, especially the dual-purpose variety.

It seems that everybody is talking about how safe grenz rays are. Don't be lulled into false security. Radiodermatitis, especially severe and pronounced telangiectasia, does result

from therapy with grenz rays, regardless of how low is the half-value layer, if the total number of roentgens is sufficiently high. The high doses which are recommended for the treatment of many inconsequential inflammatory dermatoses is sufficiently high in my opinion to cause permanent damage. I strongly advise that the same precautionary measures be employed when using grenz rays as when using x-rays.

The fundamental laws of physics apply to grenz rays as they do to superficial x-ray machines, with some variations. For example, grenz rays are absorbed more by air than conventional superficial x-rays. That means that the inverse square law does not hold 100% as it would under ideal laboratory conditions. But the inverse square law is used as a guide even when using grenz rays. It holds fairly well. If the ratio is not directly 1 to 4, then maybe it is 1 to 3 or even less. The greater the focus-target distance, the greater the variation. But to say that these fundamental physical laws pertaining to electromagnetic waves do not hold is not true. In the same way, variations of time, amperage, and voltage cause changes according to the well-known rules of electromagnetic waves. These variations are not mathematically correct as the calculations obtained under strict laboratory conditions—but a definite pattern is followed. For example, when one increases the time of exposure, the quantity of radiation is increased. The same is true when the amperage is increased. There is a relative hardening of the x-ray beam and an increase in quantity when the kilovoltage is increased. It is well to always bear these factors in mind when varying any of the factors that influence radiation dosage. Finally, there is no evidence whatsoever to lead us to believe that grenz rays affect biological material differently from x-rays except what is inherent in the quality of the beam of the ionizing radiation employed.

Dr. Charles R. Rein, New York: Unfortunately, some general practitioners and even dermatologists have purchased grenz-ray machines for the sole purpose of telling their patients that they are receiving a safe and innocuous form of therapy. At a later date, these patients may consult another dermatologist who will give x-ray therapy because they deny having received any irradiation therapy, and this could have a serious result.

Dr. C. F. Lehmann, San Antonio: I observe that the discussion has got over into the grenz-ray field. I take this paper to mean an effort towards establishing a minimal optimal technique of x-ray dosages for dermatoses. If we are to evaluate properly safe effective x-ray dosages, I think further efforts should be made to determine the lowest kilovoltage, the lowest individual dosage, the lowest total dosage given, and the time element, taking into consideration, therefore, the quality, the area treated, and the depth dose percentage.

If we are going to study this further, then I think we should select several different kilovolt ranges and keep the techniques standard, so that 10 or 20 years later, we can better study the effects of each technique, particularly the remote effects, as in the studies made by Sulzberger and his collaborators in evaluating the standard superficial x-ray therapy that has been administered over the last 20 or 25 years.

Regarding the dangers of this, for the last three years I have had available a machine with the beryllium window, with a kilovoltage range up to 100, and I have approached it with fear and trepidation, even though it has a buzzer on it to tell us that the filter is not in. I think if one uses such a machine, the technician should be checked by somebody else each time the machine is used, and, in that way, avoid these tremendous dosages that are possible if the voltage is high and the filter left out.

Regarding the effectiveness of the softer x-rays versus our standard superficial x-ray therapy, at the present day, I feel that this is comparable to handling a high-powered automobile. One can drive within the safety limits of 35 miles per hour and not get into trouble, or use all its potential power and get into trouble. I don't see any use in our using the softer rays if we can get the same effect with present-day standard superficial x-ray techniques. I can't see it, myself, unless it is an effort toward the development of x-ray therapy in which one can just use spray radiation; take the patient into a room, undress him and spray him, pop, and he's through! That may be an advance in x-ray therapy.

I think this paper will serve us more from the standpoint of evaluating the minimal amount of x-ray to be given to patients. I think the dermatologists generally have led in evaluating safe dosages of x-ray more than any other specialists; as an illustration, compare the reduced number of patients subjected to x-ray therapy now with the number subjected

to it 20 years ago. Its indications are better known, and its limitations are respected more now than formerly. I think this in itself is an indication of the conservative method of using this modality as generally practiced by dermatologists.

Dr. Maurice J. Costello, New York: All our efforts in the past 20 years have been directed toward making x-ray therapy safe. It seems to me that in the past five years, with the beryllium tube and grenz rays increasing the possibility of error, x-ray is less safe than it has been in the past.

In New York City, I have seen several cases of grenz-ray radiodermatitis similar to those that were demonstrated here by Dr. Pillsbury, severe radiodermatitis involving the anogenital regions, as a result of grenz-ray therapy, the dose of which is not easily controlled.

The whole philosophy of roentgen therapy is changing since grenz ray has been "rediscovered." Many have been convinced that grenz ray is relatively harmless and that it is safer than x-ray, indicating that they are two different rays, which of course is not true.

I have observed both acute and chronic radiodermatitis following grenz rays (also alopecia). The conclusions I came to after working for some time with grenz rays were the following: The results were faster; the beneficial effects did not last as long; recurrence was more rapid. There was no superiority over x-rays, and therefore grenz rays should not be administered because their effects were more difficult to control. In view of this, I would like to know the indications and advantages of grenz rays over roentgen rays.

I was very pleased with the report by Dr. Pillsbury. I think he told the story exactly as has been our experience in the use of this modality.

Dr. Donald M. Pillsbury, Philadelphia: I know that since this is the last scientific session, many of you are eager to get away, and I shall not attempt to comment on more than a few of the points which have been raised by the various discussers.

I should like to emphasize again that the term grenz rays means very little to the radiophysicist; and to one clinician it may mean rays of certain quality, and to another, rays of a very different quality. I would agree entirely with Dr. Cipollaro that we should regard them as very soft x-rays. It is important to indicate clearly the quality of the rays used, and the most convenient method is, of course, the H. V. L. in micra of aluminum. I think it should be pointed out in connection with Dr. Cipollaro's discussion, in which he criticized the use of very soft x-rays because of a delivery of only 3 r at a depth of 3 mm. when 100 r had been delivered to the surface, that this does not apply to all very soft x-rays. It is a perfectly simple matter, not something requiring a slide rule, to use a quality of radiation in which the depth dose at 3 mm. would be 50% or 75% of the surface dose. As has been pointed out in the paper, it is illogical, and in some respects indefensible, I think, to give even small amounts of unnecessary irradiation to normal deeper tissues, such as the vascular bed, in the treatment of a very superficial lesion of the skin. We have for years used x-rays developed at a kilovoltage of 80 or 100, sometimes with filtration, for the sake of convenience, and to some extent from force of habit. It is essential, I believe, for anyone using x-rays for therapy to become familiar with the principles of delivering proper depth doses, and to use these principles regularly. When lesions in the skin are being treated, variations of a few millimeters in the penetration of x-rays become of considerable significance.

Dr. Combes mentioned a patient with nevus flammeus who had received 27,000 r of very soft x-rays, and in whom there were no sequelae evident on examination 20 years later. He also pointed out the important fact that the statement that the patient actually received 27,000 r was only a more or less educated guess, in view of the complete lack of adequate methods of measuring these rays 20 years ago. We would estimate that our calibrations as of five or six years ago were at least plus or minus 20% in error. It is only within the last year that Dr. Reid Warren, Professor of Radiophysics in the Moore School of the University of Pennsylvania, who has done the calibration of our units, has been satisfied that the rays can be generated and measured with an accuracy roughly comparable to that obtainable with a standard superficial x-ray unit. The exact type of rays administered to the patient whom Dr. Combes mentioned is likewise unknown, unless the unit is available today for calibration by modern methods.

Dr. Sulzberger has discoursed upon the matter of sleeping better, especially if one uses very soft x-rays in place of harder irradiation. There are so many possible dangers in modern

therapeutic measures in general, that it is a little hard sometimes to select a particular cause for one's insomnia. I may say for myself that I have slept much better since discontinuing the use of standard superficial x-ray therapy for almost all benign conditions of the skin, with the exception of ringworm of the scalp. It is used occasionally for the treatment of hemangiomas, for a very occasional single plantar wart, and that is about all. We do not use x-ray therapy in psoriasis or in any type of dermatitis or fungus infection. As a result of this, I can see no lessening in the effectiveness of our over-all therapeutic result.

I realize that the advisability or inadvisability of giving x-ray therapy for benign conditions of the skin is a subject of much difference of opinion, at times amounting to rather sharp controversy. Unfortunately, I am in the position of seeing two to several patients a week who have received x-ray therapy for various benign dermatoses and who have developed mild to severe atrophic changes. In almost all of these the treatment was given at least 10 years previously, sometimes as long as 20 or 30. Some of the treatment has been given by competent radiologists, some by competent dermatologists, some of it by incompetent therapists. In spite of assurances such as those contained in Dr. Sulzberger's presentation before this Association last year, I do not believe that we can yet be certain as to what the maximum safe dose of x-ray is on the basis of 20-, 30-, or even 40-year follow-ups, especially in patients who may receive large amounts of sunlight.

I have only one comment on Dr. Andrews' discussion, namely, his statement that 200 r of very soft x-rays represented an erythema dose. This is not true with the unit we have been using. I would think, also, if I understood Dr. Andrews correctly that he has been operating his unit at a kilovoltage of 20, that the quality of the irradiation given must be considerably harder than that we have used.

As to Dr. Obermayer's discussion, it may possibly be just as well that the physicist in Southern California whom he mentions refuses to calibrate very soft x-ray units, though I worry a little bit about the general advisability of technical advisers attempting to control or suppress treatment which qualified physicians may wish to give. However, California has been well endowed with many unusual types of medical and pseudomedical therapy, and it may be advisable to delay the importation of another one for a time at least. Nevertheless, I think it should be emphasized that these units can be quite accurately calibrated at the present time, provided the kilovoltage used is not below 12.

The data we have reported represent an effort to determine whether or not very soft x-ray therapy offers any advantages in terms of safety to the patient or better therapeutic results. There is no question in our minds that such irradiation is safer; it simply does not reach as much normal tissue as do standard superficial x-rays. However, we are not greatly impressed with its permanent effectiveness as a therapeutic measure, except in a very few conditions. It is probable that our equipment will not be used very much in the future. I would anticipate that an occasional superficial epithelioma, an occasional very thin hemangioma, and an exceedingly occasional patient with dermatitis or psoriasis will be treated. We propose to follow the patients as long as possible, and since they are a stable group of private patients, it is hoped that a significant number may be seen in 10 years or more.

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CANDIDA (MONILIA) ALBICANS

Effect of Amino Acids, Glucose, pH, Chlortetracycline (Aureomycin), Dibasic Sodium and Calcium Phosphates, and Anaerobic and Aerobic Conditions on Its Growth

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FOR A LONG time it has been known that contamination or infection with Candida (Monilia) albicans exists in many conditions, some of which are malnutrition,[1] diabetes mellitus,[2] pregnancy,[3] and idiopathic hypoparathyroidism.* More recently, it has been noticed in patients receiving antibiotic therapy.† Experimentally, however, chlortetracycline (Aureomycin) has been found not to influence moniliasis in animals by Kligman,[8] while it has by Morris.[10] Skinner,[11] after reviewing 303 papers on yeast, believed that observations on the nutritional and physical changes on the morphology of Candida had been excellent but that they had been unsatisfactory from a biochemical standpoint. Reiss [12] might have been answering this challenge when he found that estrogenic and androgenic hormones, except for diethylstilbesterol, did not inhibit the growth of C. albicans and that several hormones, particularly pregnanediol, enhanced its growth.

The effect of some vitamins on the growth of the yeast has been studied. The yeast may synthesize biotin [13] but not vitamin K,[14] and biotin seems to be essential for its growth.[15] A synergistic action between biotin and thiamine has been observed.[16] Burkholder's [17] results with the use of seven vitamins would indicate that the vitamins are essential in the following order: biotin, nicotinic acid (niacin), thiamine, riboflavin, pyridoxine, pantothenic acid, and inositol. Ascorbic acid (vitamin C) was reported to be fungicidal and fungistatic by Peck and Rosenfeld.[18] No deficiency for riboflavin has been observed in yeasts,[19] and Wickerham [20] noted that species of Candida vary in their ability to synthesize certain B vitamins. Studies on the formation of acid and gas by C. albicans with various sugars have been made by Benham [21] and others, who have found this important in the identification of the candidas parasitic to man.

Other observations have shown that C. albicans increases in growth with the amount of glucose in the medium [22] and that free hydrogen sulfide in concentrations of 0.001 N or less have a killing effect on the yeast.[23] Sodium acetate is reported to

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* References 4 and 5.

† References 6 to 9.

be a weak fungicide against Candida,[24] and it is reported that extracts of human feces are toxic to yeast owing to the formic, acetic, and butyric acids contained therein.[25] The organism grows over a wide pH range, with the optimum being 7.0.‡

Dimorphism of the yeast was studied by Scherr and Weaver,[28] who found that optimum temperature favors yeast formation and below optimum temperature favors mycelia formation; yeast was present at pH 7.0 and pseudomycelia at a lower pH. Weidman [29] stated that yeast developed mycelia under adversity. A 10^{-2} molar concentration of cysteine may reduce mycelia formation,[30] and the yeast phase is maintained by the presence of glucose, according to Nickerson.[31] Skinner,[11] in his review, stated that reduced oxygen tension, starvation media, liquid media in general, high pH, and high temperature (37 C.) tend to produce mycelia phase of C. albicans. Using single amino acids, Archibald and Reiss [32] noted that Candida does not have exacting amino acid requirements and that it grows fairly well when any amino acid is present. This has not been true with other pathogenic fungi, like the faviform trichophytons,[33] Microsporum fulvum,[34] Trichophyton violaceum,[35] Trichophyton discoides,[36] Trichophyton mentagrophytes,[36] genus Microsporum,§ Trichophyton purpurem,[37] and others.

The purpose of this paper is to report various observations made by us on the growth in liquid media of C. albicans under various nutritional and physical conditions.

MATERIALS AND METHODS

A culture of C. albicans (No. 1775) ‖ was used for the stock culture, and it was kept on Sabouraud's glucose agar medium. All inoculations were made using saline suspensions of twice-washed 72-hour-old yeast cells, so that any nutrient effect of the stock medium would be minimized. The size of the inoculum, which was 0.05 cc. in all instances, was kept constant by diluting the saline suspension to make a final concentration of 20% turbidity read against distilled water in a Coleman Spectrophotometer, using 620 mμ wave length. Each cuvette measured 19 by 105 mm., and each was filled to the 10.0 cc. mark. Every tube contained sodium nitrate 0.02 gm., dibasic potassium phosphate 0.01 gm., magnesium sulfate crystals 0.005 gm., potassium chloride 0.005 gm., ferrous sulfate 0.0001 gm., and glucose 0.1 gm. This is identified as Czapek's sodium nitrate-sucrose medium, except for the quantity of glucose, which is more in the original formulation. The pH was measured with a Beckman Laboratory Model G glass electrode pH meter, and the turbidity was determined with a Coleman Electric Company Junior Spectrophotometer, using a 620 mμ filter. Our published results give the amount of light transmitted; the less the light transmitted the greater the growth. The cultures were incubated at 37 C., and all media were sterilized in an autoclave for 15 to 20 minutes at 15 lb. (6.8 kg.) pressure.

PROCEDURES AND RESULTS

The Effect of Amino Acids on the Growth of C. Albicans.—To 23 cuvettes were added Czapek's medium without sodium nitrate, inoculum, and 0.05 cc. of 1% aqueous solution of an amino acid, except for cystine and homocystine, which required hydrochloric acid for solution. The blank control for the spectrophotometer reading contained 8.85 cc. of Czapek's medium and 1.15 cc. of distilled water. The results (Table 1) are the average of three runs.

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‖ Obtained from Paulette McCormack, Department of Dermatology, Columbia University, New York.

Comment: It will be noted that no single amino acid as a nitrogen source supported growth as well as all 23 amino acids together. The effects of single amino acids in concentrations of 0.05 cc. of a 1% solution on the growth of C. albicans can be placed into three groups. A difference between the 96- and 24-hour turbidity reading of 0 to 11 was considered poor; 12 to 19, good, and 20 to 24, excellent. The amino acids which fell into the poor group were cystine, homocystine, and hydroxyproline, with ornithine being marginal. Those which were excellent were phenylalanine, arginine, aminoacetic acid, glutamic acid, tyrosine, leucine, and asparagine. Archibald and Reiss,[32] however, did not notice any exacting amino acids for Candida. The change in pH and the microscopic examination did not help to differentiate the effect of single amino acids on the growth of the yeast.

TABLE 1.—*Effects of Amino Acids on Growth of C. Albicans*

Medium	Initial pH	Turbidity Readings, Hr. 24	48	72	96	Turbidity Difference, 24-96 Hr.	Final pH	Microscopic Examination
No amino acids	8.1	94	92	91	91	3	7.15	M* = Y†
All acids	7.5	90	69	55	50	40	3.2	M > Y
Lysine	8.1	96	91	84	78	18	5.3	M > Y
Phenylalanine	8.1	95	91	83	75	20	6.1	M > Y
Tryptophan	8.0	93	86	80	77	16	6.2	M = Y
Alanine	8.1	95	89	79	77	18	5.5	M > Y
Arginine	7.9	93	85	76	72	21	5.6	M > Y
Aspartic acid	7.5	97	87	81	81	16	5.5	M > Y
Aminoacetic acid	8.0	93	86	78	72	21	5.7	M > Y
Tyrosine	7.1	99	94	85	77	22	5.6	M > Y
Cystine	7.3	98	94	92	90	8	6.3	M > Y
Threonine	8.0	97	90	85	79	18	6.6	M > Y
Glutamic acid	7.5	97	88	80	73	24	6.0	M > Y
Methionine	8.0	98	94	91	83	15	6.5	M > Y
Leucine	8.0	97	90	82	76	21	5.9	M > Y
Norleucine	8.0	95	91	86	78	17	6.5	M > Y
Isoleucine	8.1	96	92	87	82	14	6.5	M > Y
Ornithine	8.0	93	89	85	82	11	6.4	M > Y
Serine	8.0	95	88	82	78	17	6.2	Mycelia
Valine	8.0	95	89	83	78	17	6.4	M > Y
Proline	8.0	93	85	79	76	17	6.4	M > Y
Hydroxyproline	8.1	95	94	92	91	4	6.2	M = Y
Histidine monohydrochloride	7.7	93	86	80	76	17	5.9	M > Y
Homocystine	7.2	100	98	97	95	5	6.6	M = Y
Asparagine	8.0	95	85	79	70	20	5.7	M > Y

* Mycelia.
† Yeast.

Since cystine, homocystine, and hydroxyproline supported the growth of C. albicans poorly if at all in the previous experiment, two studies were made to see if these three amino acids might inhibit growth of the yeast. First, the three amino acids were omitted from Czapek's medium, which contained, instead of sodium nitrate as a nitrogen source, 1.15 cc. of a solution having 0.05 cc. of 1% solutions of all the 23 amino acids per cuvette except as noted below.

Cuvette	Initial pH	Turbidity, Hr. 24	48	72	Turbidity Difference, 24-72 Hr.	Final pH	Microscopic Examination
23 amino acids	7.4	85	56	49	36	5.0	Y > M
No amino acids	8.1	91	90	90	1	6.3	M > Y
All minus hydroxyproline	7.0	87	68	54	33	4.0	M > Y
All minus cystine	7.5	85	65	54	31	4.8	M > Y
All minus homocystine	6.9	86	68	55	31	4.7	M > Y
All minus the above three	6.8	84	69	52	32	5.0	M > Y

Comment: The differences between the turbidity readings at 24 and 72 hours indicate that cystine, homocystine, and hydroxyproline do not inhibit growth, because if they did this difference in cases in which these amino acids were eliminated singly or as a group would be greater than that of the control, in which the three were present. Since the elimination of hydroxyproline permitted greater growth than did the elimination of either cystine or homocystine, it was selected for later investigation to see if it might in certain quantities inhibit the growth of the yeast.

Then cystine, homocystine, and hydroxyproline were further evaluated by the use of Czapek's medium in which sodium nitrate was present rather than the amino acids. To the medium were added 0.05 cc. of a 1% solution of the amino acids cystine (X), homocystine (Y), and hydroxyproline (Z), according to the following tabulation.

Amino Acid	Initial pH	Turbidity, Hr. 0	24	48	72	Turbidity Difference, 0-72 Hr.	Final pH	Microscopic Examination
X	6.0	103	98	95	93	10	5.8	Y = M
Y	6.6	101	98	97	96	5	6.4	Y = M
Z	7.1	100	97	96	94	6	6.9	Y = M
X & Y	6.7	105	99	95	94	9	6.0	Y = M
X & Z	6.0	104	100	97	95	9	5.8	Y = M
Y & Z	6.6	102	98	97	95	7	6.4	Y = M
X, Y, & Z	6.8	105	98	95	92	13	6.0	Y = M
No X, Y, or Z	7.6	105	98	97	97	8	7.0	Y > M

Comment: The difference between the initial and 72-hour turbidity readings indicates that growth was better when cystine (X) was used singly or in combination than it was when homocystine (Y) and hydroxyproline (Z) were used in similar manner. When homocystine (Y) and hydroxyproline (Z) were present without cystine the growth was poorer than it was in the control (no X, Y, or Z).

Inasmuch as results with hydroxyproline in the concentrations heretofore used by us and reported by others suggested that this amino acid might inhibit the growth of C. albicans, various quantities of a 1% solution of this amino acid were added to Czapek's medium without sodium nitrate. The pH was 6.0 at the beginning of incubation and 5.8 at the end in all cuvettes.

Quantity of 1% Hydroxyproline	Turbidity, Hr. 0	24	48	72	Turbidity Difference, 0-72 Hr.	Microscopic Examination
3.0 cc.	98	92	87	84	14	Y = M
2.0	97	92	89	86	11	Y = M
1.0	98	94	92	91	7	Y = M
0.5	99	95	93	93	6	Y = M
0.1	99	95	95	93	6	Y = M
0.05	100	96	95	94	6	Y = M
0.025	99	96	95	94	5	Y = M
0.01	100	97	96	95	5	Y = M
0.0	99	97	95	94	5	Y = M

In a similar experiment, using an initial pH of 7.8 instead of 6.0, the results were comparable with those seen above, except that only yeast cells were seen microscopically at the end of 72 hours.

When various quantities of a 1% solution of hydroxyproline were added to 3.0 cc. of serum of a patient having a blood sugar level of 97 mg. per 100 cc., the following observations were made. (The pH was 7.8 initially and finally.)

Quantity of 1% Hydroxyproline	Turbidity, Hr.				Turbidity Difference, 0-72 Hr.	Microscopic Examination
	0	24	48	72		
1.0 cc.	100	85	80	80	20	M
0.25	98	85	82	81	17	M
0.1	99	83	79	78	21	M
0.05	100	87	83	83	17	M
0.01	98	88	85	85	13	M
0.0	99	89	85	85	14	M > Y

Comment: Large amounts of hydroxyproline accelerate and support rather than inhibit the growth of C. albicans, whereas small amounts have no effect. The presence of only yeast cells when the Czapek's medium had an initial pH of 7.8 is unexplainable, and so is the presence of only mycelia when serum was used. Subcultures of these mycelia grew colonies characteristic of the Candida. The failure of any change in the pH when serum was used for the medium is difficult to understand, unless it may be due to the small amount of glucose present in 3.0 cc. of serum, or that the serum proteins may buffer the solution, and/or that the H ion concentration is buffered by the system without measurable change.

The Effect of Various Quantities of Glucose on the Growth of C. Albicans.—Czapek's medium was modified by varying the amounts of glucose and by substituting for sodium nitrate a solution containing 0.05 cc. of 1% solution of each of the 23 amino acids.

Glucose, Mg. per 100 Cc.	Initial pH	Turbidity, Hr.			Turbidity Difference, 24-72 Hr.	Final pH	Microscopic Examination
		24	48	72			
1,000	7.5	82	63	55	27	4.7	M > Y
750	7.0	87	71	59	28	4.6	M > Y
500	7.9	83	66	57	26	6.9	M > Y
400	7.3	85	73	63	22	6.1	M > Y
350	7.8	84	71	62	22	6.4	M > Y
300	7.5	84	73	68	16	6.4	M > Y
250	7.3	83	72	70	13	6.4	M > Y
200	7.0	86	74	71	15	6.1	M > Y
150	7.1	86	78	76	10	6.4	M > Y
100	7.3	88	84	84	4	6.7	M > Y
75	7.6	89	87	85	4	6.9	M
50	7.4	89	87	86	3	7.0	M
0	7.5	96	93	91	5	7.4	M = Y

Comment: The growth of C. albicans was directly affected by the amount of glucose present, and so was the amount of acid formed. Glucose in concentrations of from 50 to 150 mg. per 100 cc. did not affect the growth of the yeast any more than did the blank.

Instead of a synthetic medium, 3.0 cc. of serum from a patient with a blood sugar level of 82 mg. per 100 cc. was used for the medium in each cuvette, and to each were added glucose in varying amounts, water, and inoculum.

Glucose Added, Mg. per 100 Cc.	Initial pH	Turbidity, Hr.				Turbidity Difference, 0-72 Hr.	Final pH	Microscopic Examination
		0	24	48	72			
1,000	6.8	68	35	25	20	48	6.8	M
500	6.8	71	33	29	29	42	6.8	M
250	6.8	71	35	35	33	38	6.8	M
0.0	6.8	70	57	56	55	15	6.8	M

Comment: Again, the growth of the yeast was in proportion to the amount of glucose present, but it was not attended with the formation of acid. This failure to form acid was observed by us also in the hydroxyproline experiment, when the serum was used. The presence of mycelia without yeast forms was noticed previously when serum was employed as a medium.

The Effect of Varying the pH of the Medium on the Growth of C. Albicans.—Czapek's medium was modified by substituting for sodium nitrate 1.15 cc. of a solution containing 0.05 cc. of 1% solution of each of the 23 amino acids.

Initial pH	Turbidity, Hr. 24	48	72	Turbidity Difference, 24-72 Hr.	Final pH	Microscopic Examination
2.5	97	90	81	16	2.35	Y clumps
3.4	91	76	68	23	2.7	Y clumps
5.1	92	69	56	36	3.2	Y = M
6.4	84	68	50	34	3.4	Y > M
7.4	77	56	49	28	4.3	M > Y
8.5	81	64	53	28	4.8	M > Y
9.6	77	60	50	27	5.0	M > Y

Comment: The yeast seemed to grow at all pH's, with yeast clumps being seen at extremely low levels. The change between the initial pH and the final pH was proportionately greater, depending on how high or low the initial pH was.

The Effect of Chlortetracycline on the Growth of C. Albicans.—To Czapek's medium without sodium nitrate were added 0.05 cc. of 1% solutions of all 23 amino acids and varying quantities of chlortetracycline from three different sources. One source (A) was diagnostic chlortetracycline hydrochloride (Lederle), the second (B) was 250 mg. chlortetracycline hydrochloride capsules containing calcium phosphate, and the third (C) was 250 mg. chlortetracycline hydrochloride capsules with methylparaben 90.0 mg. and propylparaben 22.5 mg.

Chlortetracycline per Cuvette, Mg.	Turbidity, Hr. 12 A	12 B	12 C	24 A	24 B	24 C	72 A	72 B	72 C	Turbidity Difference, 12-72 Hr. A	B	C
100	93	92	90	85	83	82	78	75	74	15	17	16
75	93	91	89	84	82	80	78	75	74	15	16	15
50	94	91	90	83	82	82	78	78	76	16	13	14
20	93	92	90	84	84	82	80	80	75	13	12	15
10	95	93	91	84	84	83	80	80	78	15	13	13
5	92	91	92	84	82	83	81	79	78	11	12	14
0	93	89	90	84	82	83	83	79	80	10	10	10

The pH was 7.0 before and after observation with chlortetracycline A. In chlortetracycline B and C it was 6.0 initially, and after 72 hours incubation it was 6.5 in chlortetracycline B and varied between 6.0 and 6.5 in chlortetracycline C. In chlortetracycline A the microscopic examination at 72 hours revealed mycelia to be present in greater quantities than yeast forms, and in chlortetracycline B and C the mycelia and yeast forms appeared to be equal in quantity.

Comment: Chlortetracycline A, B, or C did not inhibit the growth of C. albicans. The difference between the 12-hour and 72-hour turbidity readings suggests that there is a slight tendency for better growth to occur when the amounts of chlortetracycline B are greatest. If chlortetracycline A is a pure drug, then the antibiotic itself supports Candida growth, and the presence of dibasic calcium phosphate in chlortetracycline B added very little. Methylparaben and propylparaben in chlortetracycline C did not inhibit the growth of C. albicans.

To study further the effect of chlortetracycline on the growth of the yeast, the serum of a patient having a blood sugar level of 80 mg. per 100 cc. was used instead of Czapek's medium. Each cuvette contained 0.25 cc. of serum, inoculum, 30 mg. of chlortetracycline, A, B, or C, and distilled water to bring the total content in each cuvette to 10.0 cc.

Chlortetracycline	Initial pH	Turbidity, Hr.			Turbidity Difference, 0-72 Hr.	Final pH
		0	48	72		
A	6.5	92	87	86	6	6.0
B	6.5	91	89	89	2	6.0
C	6.5	90	89	89	1	6.0
Control	7.0	90	89	89	1	6.5

The microscopic examination revealed yeast to be more numerous than mycelia at the end of 72 hours' growth in all cuvettes.

Comment: Chlortetracycline diagnostic (A) supported growth, while there was no change in the others. The drop in pH in all cuvettes was unusual, because when serum had been previously used by us for medium no change in pH had occurred. Human serum decreases chlortetracycline activity, and this appears to have occurred in this case.

Since others investigating the effect of chlortetracycline on the growth of C. albicans have also studied the effect of dibasic sodium and calcium phosphates, this was done by us. A 1% solution of dibasic sodium phosphate was added in different quantities to Czapek's medium without sodium nitrate.

$CaHPO_4$, Mg. per Cuvette	Initial pH	Turbidity, Hr.			Turbidity Difference, 0-72 Hr.	Final pH	Microscopic Examination
		0	24	72			
10	7.6	88	86	84	4	7.1	Y > M
9.0	7.5	90	88	86	4	7.0	Y > M
7.0	7.5	94	92	90	4	7.0	Y > M
5.0	7.3	96	93	90	6	6.8	Y = M
0.0	6.7	99	97	95	4	6.0	Y = M

When varying quantities of dibasic sodium phosphate were added to 3.0 cc. of serum of a patient having a blood sugar of 82 mg. per 100 cc., the growth was better than it was in the control, and the same occurred whether 10.0 mg. or 2.5 mg. of dibasic sodium phosphate was used.

Dibasic calcium phosphate was added without sterilization in different quantities to Czapek's medium without sodium nitrate.

$NaHPO_4$, Mg. per Cuvette	Initial pH	Turbidity, Hr.			Turbidity Difference, 0-72 Hr.	Final pH	Microscopic Examination
		0	24	72			
10	6.6	71	70	65	6	6.2	Y > M
9.0	6.5	71	71	62	9	6.1	Y > M
8.0	6.5	74	73	62	12	6.1	Y > M
7.0	6.6	77	76	73	4	6.2	Y > M
5.0	6.2	82	81	77	5	6.0	Y > M
0.0	6.7	98	96	94	4	5.8	Y > M

Comment: The differences between turbidity readings show that dibasic sodium phosphate does not alter the growth of the yeast in Czapek's medium without a nitrogen source. When serum was used for the medium, growth was improved with dibasic sodium phosphate, and the same effect was obtained with 2.5 mg. and 10.0 mg.

Dibasic calcium phosphate caused sufficient turbidity to make the readings difficult. The differential readings of 9 and 12 suggest that this salt accelerated the

growth of C. albicans. The growth factor must be the calcium rather than the phosphate, since the sodium salt of the phosphate gave no growth in the same medium.

The Effect of Aerobic and Anaerobic Conditions on the Growth of Candida Albicans.—Experiment 1: Four 125.0 cc. Erlenmeyer flasks were prepared with inoculum and 30 cc. of medium. To create aerobic conditions two of the flasks were shaken continuously in a rotary shaker during the period of 24-hour observation, and to create anaerobic conditions the other two were not shaken.

	Turbidity, at 24 Hr.	Microscopic Examination
Shaken		
1. Nutrient broth medium with 0.5% glucose	9	Y > M
2. Nutrient broth medium	34	Y = M
Not shaken		
3. Nutrient broth medium with 0.5% glucose	36	Y = M
4. Nutrient broth medium	81	M > Y

Experiment 2: Since glucose seemed to be so important in the above experiment, there were added to two 125.0 cc. Erlenmeyer flasks 30.0 cc. of 0.5% glucose in distilled water and an inoculum. One flask was shaken continuously, and the other was not.

	Turbidity, Hr.		Microscopic Examination
	24	48	
1. Shaken (aerobic)	68	69	Y = M
2. Not shaken (anaerobic)	82	72	M > Y

Experiment 3: To two other 125.0 cc. Erlenmeyer flasks were added 50.0 cc. of Czapek's medium and inoculum. One flask was not shaken, and the other was.

	Turbidity, Hr.				
	24	48	72	96	168
1. Shaken (aerobic)	97	95	93	91	85
2. Not shaken (anaerobic)	96	93	91	90	80

Comment: The effect of shaking on the growth of C. albicans differs with the medium used. This in part is due to the glucose present, as noted in Experiment 1, in which the broth medium with glucose grew C. albicans much better than the one without glucose. The fact that Czapek's medium was not affected by shaking led us to do all our studies with this medium without shaking.

GENERAL COMMENT

The growth of C. albicans differs considerably when the same quantities of 23 different amino acids are added singly to a medium like Czapek's. The amino acids which seemed to support growth poorly were crystine, homocystine, and hydroxyproline, with ornithine being marginal. Those which supported growth exceptionally well were phenylalanine, arginine, aminoacetic acid, glutamic acid, tyrosine, leucine, and asparagine. The amino acids which gave good growth were lysine, tryptophane, alanine, aspartic acid, threonine, methionine, norleucine, isoleucine, serine, valine, proline, and histidine monohydrochloride. Archibald and Reiss [32] did not find this marked difference in the effect of various amino acids on the growth of C. albicans. Of the three amino acids which supported growth poorly, cystine was found to be the most active. Hydroxyproline in large amounts supported the growth of the yeast, whereas no effect was noted with small amounts. We wonder whether

others,¶ except for Bereston # and also Robbins and McVeigh,[37] who have felt that hydroxyproline inhibited the growth of certain fungi, have tried the effect of large amounts of the amino acid. Certainly, use of small amounts of hydroxyproline would indicate that this amino acid either does not support the growth of C. albicans or that it inhibits growth. T. purpureum was stimulated by small amounts of hydroxyproline and inhibited by large amounts in the hands of Robbins and McVeigh,[37] and several strains of the genus Microsporum were inhibited by 4.0 gm. of hydroxyproline per liter in Bereston's study.*

Glucose affected the growth of C. albicans directly as the amount of glucose was increased in Czapek's medium or in serum. This favorable effect became apparent when glucose equivalent to 150 mg. per 100 cc. or more was present. Acid was formed in proportion to the amount of glucose used.

Varying the pH of the Czapek's medium revealed that the yeast grew at pH from 2.5 to 9.6, and that the best growth was in the range of 5.1 to 6.4. Talice [28] found optimum growth at pH 7.0.

Chlortetracycline diagnostic and chlortetracycline capsules with calcium phosphate accelerated growth slightly when compared with the control, and the growth was better when the concentrations of the antibiotic were highest. If our information is correct that chlortetracycline diagnostic contains only the antibiotic, then our observations agree with the report of Huppert and others [25] and Morris [10] and disagree with Lipnik and his associates,[39] who stated that the phosphate contained in chlortetracycline capsules accelerated growth and not chlortetracycline itself. Dibasic calcium phosphate also accelerated the growth of C. albicans in our experiments. Methylparaben and propylparaben in chlortetracycline capsules did not stop the growth of the yeast, since if they did the growth when these two compounds was present should have been less than in the control. This observation is not supported by the work of McVay and Sprunt.[40]

Lipnik and his associates [39] have shown that dibasic sodium phosphate will stimulate the growth of the yeast, and this parallels our findings with one medium and not with another. Since Czapek's medium without sodium nitrate supported growth when dibasic calcium phosphate was added and not with dibasic sodium phosphate, it would appear that the calcium was more important than the sodium or the phosphate. Lipnik and his associates [39] felt that inasmuch as calcium chloride did not alter the growth of C. albicans while dibasic calcium phosphate did, the phosphate was responsible for stimulation. It would appear that the differences in conclusions arise owing to results obtained with the use of different media.

The microscopic examinations showed dimorphism, which Scherr and Weaver [28] stated was due to altered temperature, and this we kept constant. They reported also that the yeast phase was present at pH 7.0 and pseudomycelia at lower pH's. Skinner [11], however, found mycelia formation with high pH's, a finding which our studies on pH support. He noticed that reduced oxygen tension favored mycelia formation, which was also seen by us in the anaerobic and aerobic investigation. Mycelia formation, according to Skinner,[11] occurred when liquid media were used

¶ References 32-36.

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* Bereston, E. S.: The Vitamin, Amino Acid and Growth Requirements of the Genus Microsporum, to be published.

and when a temperature of 37 C. was utilized. Both these conditions were present in our studies and may account for the absence of pure yeast, except in a few instances. Starvation diet has been shown to favor mycelia formation,[11] and this seems to be the picture in most of our studies, since mycelia usually outnumbered yeast. Nickerson[31] demonstrated that glucose was important for the presence of the yeast phase. This was not confirmed by us. Weidman[29] also believes that yeast develops mycelia under adversity.

SUMMARY AND CONCLUSIONS

1. Liquid medium has been found to be a convenient way to study the growth of Candida albicans, since growth can be measured by determining the turbidity changes of the medium.

2. Like quantities of single amino acids vary in their ability to support the growth of C. albicans.

3. Hydroxyproline in large amounts accelerates rather than inhibits the growth of the yeast.

4. Glucose accelerates the growth of C. albicans in direct proportion to the amount of glucose present when quantities greater than 150 per 100 cc. are added.

5. The yeast grows at all pH's and best in a range between 5.1 and 6.4.

6. Chlortetracycline (Aureomycin) supports the growth of C. albicans, and methylparaben and propylparaben do not inhibit the growth of the yeast.

7. In Czapek's medium without sodium nitrate, dibasic calcium phosphate makes yeast grow, whereas dibasic sodium phosphate does not.

8. C. albicans grows better in aerobic than anaerobic conditions, and this is dependent upon the medium employed.

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ABSTRACT OF DISCUSSION

DR. GEORGE M. LEWIS, New York: This excellent study by Johnson and his co-workers represents a great deal of work, is basic, and further confirms the known ability of C. albicans to grow as a facultative organism. It colonizes well on almost all laboratory mediums on a wide range of pH values. It is also of interest that this fungus utilizes any one or, even better, a mixture of amino acids and any of the carbohydrates, its best growth appearing when plentiful sugar is available.

The authors agree with the majority of investigators, who believe that chlortetracycline has a direct stimulating effect on the growth of C. albicans and that this effect is not due to phosphate contained in chlortetracycline capsules, as has been suggested.

The utilization of a spectrophotometer to measure quantitatively the growth in a liquid medium by estimation of the degree of turbidity appeals to me as being a very accurate method. Controlled conditions were carefully set up and appear to have been meticulously employed. Further study may explain the variable mycologic findings of either yeast cells alone, a comixture with mycelium, or mycelium alone, according to the pH of the medium and the presence of higher percentages of active ingredients. At the moment, such data are interesting.

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SYNTHETIC ANTIMALARIAL DRUGS IN CHRONIC DISCOID LUPUS ERYTHEMATOSUS AND LIGHT ERUPTIONS

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PROMISING results with the use of quinacrine (Mepacrine; Atabrine) in chronic discoid lupus erythematosus were reported in 1951 by Page.[1] His findings have, in the main, been confirmed by subsequent investigators.* A recent paper [5] quotes a report by Popoff & Kutinscheff who presented six cases so treated at a meeting of the Sofia Dermatological Society in 1941.

In the study herein reported it was decided to treat not only chronic discoid lupus erythematosus but also light eruptions of the summer prurigo type with a series of synthetic antimalarial drugs. Both diseases in this area show a similar seasonal incidence, and after preliminary trials it was decided to treat all cases in the summer of 1952 with quinacrine (3-chloro-7-methoxy-9-[1 methyl-4-diethylaminobutylamino] acridine dihydrochloride) and those in the summer of 1953 with chloroquine (7-chloro-4-[4-diethylamino-1-methylbutylamino] quinoline) diphosphate. Primaquine (8-[4-amino-1-methylbutylamino]-6-methoxyquinoline) diphosphate had also been tried in two cases in our preliminary trials, but since both patients complained of giddiness and headache on low-dosage therapy its further use was abandoned.

We present now the results of treatment as assessed in October, 1953. In the quinacrine series it is possible to give not only the immediate response to treatment but also a follow-up assessment a year later.

DOSAGE SCHEDULE

Quinacrine.—The majority of patients received 0.1 gm. three times daily for one month, then 0.1 gm. twice daily for the next month, and finally 0.1 gm. daily for the remainder of the treatment period. Duration of treatment varied from 4 weeks (total 8.4 gm.) to 38 weeks (total 35 gm.).

Chloroquine.—The usual dose of this drug was 0.25 gm. once daily. Some cases received 0.25 gm. twice daily over a short period, but side-effects, which are discussed later, were common at this dosage level. In the case of chloroquine, the drug was given on week days only, and the majority of the patients had Saturday and Sunday free of medication. Duration of treatment varied from 3 weeks (total 3.75 gm.) to 34 weeks (total 42.5 gm.).

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* References 1 to 8.

CHRONIC DISCOID LUPUS ERYTHEMATOSUS

Table 1 compares the immediate results after quinacrine therapy with those obtained after treatment with chloroquine.

Figure 1 illustrates an erythematous case "cleared" with quinacrine. Figure 2 shows a "much improved" result with chloroquine in a case presenting scaly infiltrated plaques of long duration.

It will be seen that the immediate results with quinacrine and chloroquine are essentially similar. While the figures for the quinacrine series support the results of previous investigators in respect of the immediate effect of therapy, Table 2, which summarizes the assessment made of the quinacrine-treated cases at the beginning of the next summer, shows a high relapse rate.

TABLE 1.—*Immediate Results After Quinacrine Therapy Compared with Those After Chloroquine*

Drug Used	Number of Patients	Defaulted	Number Clear *	Number Much Improved *	Number Improved *	Number Not Improved *
Quinacrine	45	2	17	7	18	1
Chloroquine	45	2	16	14	9	4

* The term "clear" signifies complete disappearance of all lesions. "Much improved" signifies considerable improvement with or without the disappearance of some lesions. "Improved" signifies definite but minor improvement.

TABLE 2.—*Condition of Patients in 1953 Compared with That Before Treatment in 1952*

Immediate Response After Mepacrine 1952	Number of Patients	Assessment May, 1953			
		Clear	Much Improved	Improved	Not Improved
Clear	17	9	1	..	7
Much improved	7	1*	2	..	4
Improved	18	..	1	6	11
Total	42	10	4	6	22

* This patient had had a small residual patch treated with CO_2-acetone slush before this assessment.

It should be noted that 18 of the 22 cases treated with quinacrine in 1952 but assessed as "not improved" in May, 1953, were then treated with chloroquine. These cases are included in Table 1, but when the immediate response of the same case to each drug in turn was assessed it was noted that of six cases "cleared" with quinacrine, four were "cleared" with chloroquine, one "improved" and one "not "improved." Four cases "much improved" by quinacrine showed the same clinical response to chloroquine. Of eight cases "improved" by quinacrine, two were "cleared" by chloroquine, four "much improved" and two "improved."

LIGHT ERUPTIONS

Under the same dosage schedule 17 cases of light-sensitive summer eruption were treated in 1952 with quinacrine. Of these 17 cases, 1 was controlled in that the eruption disappeared and remained quiescent during the summer months; 12 cases were improved in that the condition, though still present, was much less severe than at the same time during the previous years; 4 cases were not influenced by quinacrine therapy.

Fig. 1.—Erythematous type of chronic discoid lupus erythematosus, duration two years. Left, before treatment with quinacrine. Right, after two months' treatment with quinacrine.

Fig. 2.—Chronic discoid lupus erythematosus, duration 26 years. Left, before treatment with chloroquine. Right, after one month's treatment with chloroquine.

In May, 1953, all the above cases that could be traced were again showing a seasonal recurrence of the summer eruption. Those who attended, together with any new cases seen, were treated in the summer of 1953 with chloroquine in the same dosage as that detailed for chronic discoid lupus erythematosus. Twenty-four cases were so treated. Eight were controlled; 11 were improved in comparison with their untreated status, and 5 cases were not influenced by chloroquine therapy.

When the two forms of therapy are compared, it will be seen that chloroquine appears to be more effective than quinacrine in controlling summer eruptions.

SIDE-EFFECTS OF QUINACRINE AND CHLOROQUINE

With quinacrine, in this study the incidence of side-effects was extremely low. Most patients exhibited staining of the skin. A few complained of nausea when the dosage was at a high level, but in no case did therapy have to be abandoned for this reason. No patient developed a drug eruption from quinacrine, but when large numbers are treated with this drug this complication will probably appear.† With chloroquine the incidence of side-effects has been higher. In preliminary trials with 0.25 gm. twice daily some patents developed blurring of vision. However, on 0.25 gm. daily the side-effects were seldom of such magnitude as to interrupt treatment. Isolated instances of headache, nausea, giddiness, and abdominal pain were noted. One patient produced an erythema-multiforme-like eruption, which disappeared during treatment. Another, aged 35, developed an acneform eruption of the back and arms which subsided after chloroquine was discontinued. Perhaps of greater interest is the fact that several patients taking chloroquine showed a tendency to develop staphylococcal lesions, such as furuncles and styes.

COMMENT

The initial reason for our investigation into the use of other synthetic antimalarial drugs in the treatment of chronic discoid lupus erythematosus was the staining of the skin which occurs with quinacrine therapy. Although all our patients were warned about this side-effect and the majority were willing to tolerate it when improvement in the skin lesions was evident, several did raise objection to the yellow color. One unfortunate woman was asked to leave her employment despite her protestations that she was not suffering from "jaundice." In some cases the yellow staining appeared to be localized to the exposed areas, but with Wood's light a generalized fluorescence was evident. We were unable to relate the clinical response to the degree of staining of the skin,‡ nor could any increase in fluorescence in the lesions, as opposed to the unaffected skin, be detected.[5]

Patients under treatment with chloroquine show no staining of the skin, nor is there any fluorescence of the skin under Wood's light.

Page [1] stated that quinacrine might act by reducing light sensitivity of the skin. Although our cases of light sensitivity treated in 1952 with quinacrine showed an encouraging degree of improvement, the results with chloroquine in 1953 indicate that this drug is more effective. The fact that chloroquine, a colorless drug, produced results similar to those of quinacrine in the treatment of light sensitivity and chronic

† References 9 and 10.

‡ References 1, 2, 3, 7, and 8.

discoid lupus erythematosus, would seem to dispose of the theory that quinacrine acts directly by screening out the blue portion of the spectrum. Miller and his associates [11] found no change in the sensitivity of the skin in volunteers subjected to measured doses of ultraviolet radiation before and after taking quinacrine. Experimental work has shown that quinacrine fails to protect rats from chemically induced light sensitivity.§

Chloroquine is a direct development of quinacrine, the same basic side chain being attached to a quinoline instead of to an acridine nucleus. In addition to antimalarial activity, both compounds are capable of inhibiting the action of adenosine on the heart,[12] as can quinine.‖ Page [1] has suggested that quinacrine might act by antagonizing adenyl compounds produced in the local or generalized lesions of lupus erythematosus. The fact that chloroquine, which also antagonizes adenosine, has been shown to be an effective drug in the treatment of chronic discoid lupus erythematosus, would appear to support the hypothesis.

We have not been able to demonstrate that either the duration of the disease before treatment or the nature of previous therapy influences the response of chronic discoid lupus erythematosus to these antimalarial drugs. The type of lesion present did not seem to influence the eventual response, although, as might be expected, erythematous lesions responded more quickly than the scaly infiltrated plaques or cases in which scarring was already a feature.

During the period under review two cases of acute disseminated lupus erythematosus were treated with quinacrine for short periods without success. Chloroquine therapy has not been attempted in this systemic type of the disease.

In our cases the incidence of toxic side-effects has been low, and any untoward symptoms have been easily controlled by adjusting the dose of the drug. It must be emphasized, however, that the possibility of severe toxic effects from quinacrine and from chloroquine does exist, and we feel that these drugs, although they have the advantage of ease of administration, should still be given under strict supervision. We consider that further experience with chloroquine may prove that it can replace quinacrine in the treatment of chronic discoid lupus erythematosus.

Although comparable figures for relapse after treatment with chloroquine are not yet available, there is no evidence to suggest that its therapeutic effect will be any more permanent than that of quinacrine.

SUMMARY

A comparative study of the treatment of chronic discoid lupus erythematosus and light-sensitive summer eruptions with quinacrine and chloroquine is described.

Results are detailed, and it is concluded that chloroquine is as effective as quinacrine in controlling these conditions.

The implications of these clinical findings on theories of the mode of action of quinacrine in chronic discoid lupus erythematosus are discussed.

Imperial Chemicals (Pharmaceuticals) Ltd. supplied the antimalarial drugs mentioned in this study.

§ Green, K. G.: Personal communication to the authors.

‖ Wevill, L. B.: Personal communication to the authors.

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REVIEW OF THE PATHOGENESIS AND ALLERGIC ASPECTS OF COLLAGEN DISEASES

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KLEMPERER, Pollack, and Baehr [1] in 1941 described the basic pathology of disseminated lupus erythematosus as a systemic alteration of the extracellular elements of the connective tissue. This alteration consisted mainly in a mucoid and fibrinoid degeneration of the ground substance and the collagen fibers. They later pointed out [2] that there were other diseases that exhibited similar widespread alterations in connective tissue, and that there might be pathogenetic significance in the fact that these diseases all had a common anatomic site; that they were, in fact, diseases of the connective tissue system. They were designated as the "collagen diseases," and the list has grown from the original disseminated lupus erythematosus and generalized scleroderma to include rheumatic fever, rheumatoid arthritis, dermatomyositis, periarteritis nodosa, and serum sickness. The authors were quick to point out that by linking these obviously heterogeneous diseases together they did not mean to define them as such, but merely to indicate the similarities in pathological change, and perhaps give a clue to a common denominator that would make for a better understanding of the processes involved. In their original paper Klemperer and his associates stated as follows:

> It must become quite clear that one may regard the connective tissues of the body . . . as a well-defined, widely dispersed system liable to a variety of injuries. We are concerned here only with those processes which affect the system in its entirety. . . . However, to identify this system as a seat of certain diseases is by no means to identify these diseases with one another or even to relate them. This would be unjustifiable oversimplification.

In spite of this note of caution some investigators and practitioners have drawn unwarranted conclusions as to the diagnostic and etiologic significance of this concept. There still is a real danger of the term "collagen disease" being used as a catchall to include diseases of obscure etiology, thereby to stifle the new avenues of approach to the study of the mechanisms and processes involved in these alterations of the connective tissue system.

Klinge,[3] in 1933, described the basic pathology of rheumatic fever and rheumatoid arthritis as a systemic involvement of the entire connective tissues of the body, with fibrinoid degeneration of the collagenous tissue and myxomatous swelling of the ground substance as the prominent features. The finding of

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similar connective tissue changes in rabbits rendered hypersensitive to foreign protein led Klinge to the conclusion that the comparable changes seen in the rheumatic diseases were also the expression of a hypersensitivity reaction. He further suggested that other diseases exhibiting these fibrinoid changes, namely, periarteritis nodosa, dermatomyositis, malignant nephrosclerosis, thromboangiitis obliterans, certain nephritides, and subacute bacterial endocarditis, were also due to hypersensitivity. In 1938 Masugi and Ya-Shu [4] included scleroderma in this group after noticing widespread fibrinoid vascular lesions in this disease.

However, when Klemperer, Pollack, and Baehr noted similar fibrinoid changes in disseminated lupus erythematosus, they were reluctant to ascribe them to hypersensitivity, realizing that fibrinoid alteration was not exclusively a product of hypersensitivity: that it had been described at the bases of peptic ulcers; as a result of mechanical injury in the skin of the rat, and in experimental hypertension.* Later work proved that fibrinoid changes could be produced experimentally in other nonallergic conditions. While admitting a possible hypersensitivity factor in some of these diseases, Klemperer and his associates rejected it as an explanation for all fibrinoid alteration. They emphasized that what was described as fibrinoid change was not a precise chemical definition but a comparatively gross feature, one that could conceivably be caused by many different chemical changes still obscure on account of the inadequacy of our histochemical methods. Progress in understanding the pathogenesis of these diseases could be advanced only by an exhaustive study of the physiological factors responsible for, and the chemical nature of, the fibrinoid alterations in each one of these diseases.

FIBRINOID DEGENERATION

The term fibrinoid degeneration was coined by Neumann in 1896 to describe the deposition of a homogeneous, eosinophilic, refractive band-like material found in the connective tissue in certain conditions. It has long been believed that this substance, which resembled fibrin in structure and staining qualities, represented either a product of disintegrating and degenerated collagen fibers or a deposition of fibrin on the intact collagen fiber. This view was still prevalent at the time the concept of "collagen disease" was formed and accounts for the term "collagen diseases." However, recent work seems to indicate that the ground substance, rather than the collagen fibers, is the seat of the pathologic change. Klinge was the first to consider the ground substance as the putative site of fibrinoid degeneration, and more recent work by Altshuler and Augevine [5] suggests that fibrinoid changes may be the result of precipitation of the acid mucopolysaccharides in the ground substance.

Recognition that the ground substance may play an important role in pathogenesis of systemic diseases stimulated an intensive study of the chemical nature and physiological disciplines of this long-neglected component of the connective tissue.

PHYSIOLOGICAL FACTORS CONTROLLING THE GROUND SUBSTANCE

Although the ground substance had for many years been known to be mucinous in nature, Karl Meyer [7] and others have firmly established that it contains acid mucopolysaccharides linked to proteins; that these mucopolysaccharides are mainly

* References 5 and 6.

hyaluronic acid and chondroitin-sulphuric acid; that there exist hyaluronidases or enzymes that depolymerize these substances and antihyaluronidases and specific inhibitors which retard depolymerization. The influence of hormones on this regulation has been demonstrated by study of the opposing effects of luteinizing and follicular hormones upon the spreading of dyes in rabbit skin.[8] There is evidence that testosterone stimulates the production of ground substance of the cock's comb,[9] and estrogens have a similar action on the sex skin of monkeys.[10] The effects of the adrenal steroids is now of special interest because of the significant response of some of the "collagen diseases" to these drugs. Desoxycorticosterone acetate greatly enhances osmosis of semipermeable membranes in vitro and of synovia in vivo, while cortisone suppresses it. Likewise, the increase in permeability of capillaries induced by hyaluronidase is suppressed by cortisone.†

Vitamin C plays a role in the growth and healthy maintenance of connective tissue as evidenced by the fact that in the absence of Vitamin C no collagen is laid down, and the fibroblasts show fatty degeneration and reduced activity.‡ Wolbach and Bessey [16] believe that ascorbic acid or its derivative is an integer of collagen, and Meyer [17] is of the opinion that it is an essential component of chondroitin-sulphuric acid. Reppert, Donegan, and Hines [18] have presented evidence that it acts by inhibiting the hyaluronidase-hyaluronic acid reaction.

With so many and varied factors playing a role in the physiological maintenance of connective tissue, it is evident that pathologic changes may result from a variety of causes. The fact that the "gross" pathologic picture which we call fibrinoid degeneration is the result of all these causes does not mean that the steps leading to this end-result are necessarily similar. Moreover, it is wrong to assume that the "fibrinoid" changes are identical in all the collagen diseases, while to ascribe an all-inclusive cause for these changes is but to cloud the issue and delay progress in the search for the etiologic factors and pathogenesis of these diseases.

DISSEMINATED LUPUS ERYTHEMATOSUS

It would be far beyond the scope of this paper to review the important and extensive investigations along these lines in all the collagen diseases. However, a brief summary of the advances made in the study of the pathogenesis of disseminated lupus erythematosus will demonstrate how far our knowledge of the condition has increased as a result of recent investigations of the fibrinoid material in this disease.

It is an amazing fact that, although acute disseminated lupus erythematosus was described by Kaposi in 1872, it was not until 1924 that the first significant contribution to the systemic pathology of this disease was made. In that year, Libman and Sacks [19] described a previously unknown form of endocarditis. Although they originally believed that their cases represented a new entity, it was soon pointed out by Belote and Rattner,[20] and again by Keil,[21] and finally by Libman [22] himself that the endocardial lesions were in reality part of the picture of systemic lupus erythematosus.

It seems rather incomprehensible to us that the systemic alterations in this disease so long eluded recognition by the pathologist. But the belief, once prevalent,

† References 11 and 12.

‡ References 13 and 14.

that lupus erythematosus was a disease strictly of the skin, and that the acute symptoms were merely an expression of "toxicity" apparently discouraged careful scrutiny. Also, the mistaken idea of its tuberculous origin limited pathological investigations at that time to attempts at proving (or disproving) a tuberculous etiology.

Libman and Sacks in their original work also described periarterial follicular sclerosis in the spleen and hematoxylin-stained bodies in the endocardial vegetations. These hematoxylin-stained bodies were shown to be specific for disseminated lupus erythematosus by Gross [23] in 1932, and were found in other organs first by Ginzler and Fox,[24] and later by Klemperer, Pollack, and Baehr.[1] Renewed interest of the general pathologist in the systemic manifestations in this disease resulted further in the description by Baehr, Klemperer, and Schifrin [25] of conspicuous changes in the vessels, in the serosal coats, and in synovial membranes, which led them to suggest that the endothelium might be "the site of attack of a noxa in a broad sense." These conclusions were quickly discarded, however, when subsequent investigations on old and new cases revealed the fibrinoid alteration of the extracellular components of connective tissue. Mesenchymal elements being an integral part of all organs of the body, it was possible to explain the morphological changes previously described in varied parts (the skin, vessels and other tissues), as the result of widespread disturbance of the connective tissue system.

It was after discovery of this systemic fibrinoid alteration that the theory of hypersensitivity causation was applied to acute disseminated lupus erythematosus. Exponents of this theory pointed out that these alterations were similar to the changes produced by the injection of foreign protein in rabbits, to the changes seen in serum sickness, periarteritis nodosa, and the rheumatic diseases. This reasoning was further substantiated by the finding of elevated gamma globulins and the beneficial effects of cortisone in lupus erythematosus. However, the discovery of the L. E. cell by Hargraves, Richmond, and Morton [26] and of the L. E. serum factor by Haserick,[27] as well as the demonstration of specific hematoxylin bodies in several organs, definitely separated lupus erythematosus from the other so-called "allergic" diseases.

These important discoveries have also demonstrated that at least some of the fibrinoid alterations in acute disseminated lupus erythematosus are of different chemical nature that those seen in other "collagen diseases." The specificity of the L. E. cell, the hematoxylin bodies, and the L. E. serum factor seemed to offer the first important clues to the pathogenesis of disseminated lupus erythematosus and at first appeared to be entirely unrelated to the fibrinoid alterations previously noted in the connective tissue. However, cytochemical investigation by the Mount Sinai group revealed that the hematoxylin bodies contained depolymerized deoxyribose nucleic acid. Morphologic resemblance between the hematoxylin bodies and the Hargraves L. E. cell led Lee, Michael, and Vural to cytochemical study of the L. E. cells. These authors [28] found that they were optically and chemically identical with the hematoxylin bodies and that they also contained deoxyribose nucleic acid. These facts would seem to indicate that the L. E. factor, traced to the gamma globulin fraction by Haserick, is related to depolymerization of deoxyribose nucleic acid in the tissues. There is further evidence that the hyalin thrombi seen within the glomerular capillaries in disseminated lupus erythematosus, and believed to consist

of fibrinoid material, are also faintly Feulgen-positive and contain the residue of broken-down nucleoproteins, the result of progressive depolymerization of desoxyribose nucleic acid. Because the L. E. factor, which is believed to produce this depolymerization, is specific for disseminated lupus erythematosus, it is concluded that at least some of the fibrinoid alterations (which are the result of this depolymerization) are peculiar to lupus erythematosus and differ chemically from the "fibrinoid" of the other "collagen diseases."§

Thus a new avenue of approach to the pathogenesis of systemic lupus erythematosus has been opened by the discovery of the specific breakdown of nucleoproteins in this disease. Investigations into the mechanism of action of the L. E. factor in this connection promise further advances in our knowledge of this disease and further separation from the all-embracing and rather obscure concept of the disease as a hypersensitivity reaction.

PERIARTERITIS NODOSA

Attempts to explain periarteritis nodosa on a hypersensitivity basis dates from 1925, when Gruber [29] suggested that no one specific agent was the cause of this disease, but that it might be the result of a general systemic hyperergic reaction to a variety of infectious and toxic agents. The original pathologic criterion for the diagnosis of this disease, as described by Kussmaul and Maier [30] in 1866, was the presence of palpable nodules along the courses of many small arteries throughout the body. Microscopically, the nodules consisted of accumulations of inflammatory and connective tissue cells in foci of degeneration within the vessel walls. Until the beginning of this century all the reported cases of periarteritis nodosa demonstrated these macroscopic nodules along the small arteries. In 1903 Vezprémi and Jancsó [31] reported a case in which there were no gross nodules, but which showed microscopically the characteristic necrotizing arteritis seen in the previously reported cases. With the acceptance of the criteria of microscopy for the diagnosis of periarteritis nodosa, the number of reported cases rapidly increased. Experimental reproduction by Klinge,[32] Vaubel,[33] and later by Rich [34] in this country, of necrotizing arteritis in animals rendered hypersensitive to foreign protein, together with the occurrence of other allergic manifestations in some cases, and the demonstration again by Rich [35] of the development of periarteritis nodosa lesions in cases of drug hypersensitivity, lent weight to the concept of the allergic origin of this disease, which has received wide acceptance.

There seems to be no doubt that hypersensitivity can cause necrotizing lesions of the vessels. However, may we say with the same degree of assuredness that the reverse also holds true, namely, that all necrotizing arteritis is the result of hypersensitivity? Recent work would not so indicate. Holman [36] has produced necrotizing arteritis in dogs by a combination of high-fat diet and artificially induced renal insufficiency. In some of these animals hypertension developed but was not necessary for the development of the arteritis. Hypertension alone can cause necrotizing lesions of the vessels. Cases are reported of these lesions occurring in persons dying of a malignant hypertension.[37] Masson and his associates [38] produced these lesions in rats by inducing hypertension experimentally.

§ Klemperer, P.: Personal communication to the author.

Necrotizing arteritis, then, can be produced by a variety of agents. Hypersensitivity is certainly one cause; hypertension is another, and there are undoubtedly still more. Cases reported in the literature as periarteritis nodosa because of the microscopic changes in the vessels must be reanalyzed and reclassified, on the basis of stricter and more specific criteria, before progress can be made in the study of its pathogenesis. This Zeek [39] has attempted to do in her recent excellent review. She has classified the reported cases under the main heading of "Necrotizing Angiitides," and with good cause separates them into five categories: (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa, and (5) temporal arteritis.

Adherents to the theory that hypersensitivity is important in the pathogenesis of rheumatic fever are many, but since it is not of dermatologic interest the subject will not be discussed here.

There is no convincing evidence that a hypersensitivity factor plays a role in the other collagen diseases: generalized scleroderma, dermatomyositis, and rheumatoid arthritis. Klinge's original inclusion of these obscure maladies among his "hyperergic diseases" on the basis of their fibrinoid connective tissue changes has not been sustained for reasons previously discussed. Advances in the study of the pathogenesis of these diseases have been slow and there are few promising leads. It seems reasonable to suppose, however, that patient investigation of the chemical and physiologic processes involved in their systemic connective tissue alterations will further advance our knowledge in these diseases as it has in the other "collagenoses."

CONCLUSION

In conclusion, we believe that the concept of the "collagen diseases" has been of inestimable value in furthering our knowledge of these obscure diseases for the following reasons:

1. It has opened our eyes to the fact that the connective tissue, far from being an inert and unimportant mechanical cement substance, is a dynamic, labile, and important element of the body structure, subject to control and maintenance by many factors, including hormones, enzymes, and vitamins.

2. It has pointed out that pathological deviations of these controls can cause extensive connective tissue changes which because of their widespread distribution can result in a variety of symptoms and lead to the development of varied and heterogeneous diseases.

3. Far from grouping together heterogeneous diseases, a criticism levelled by some, it has separated many of these diseases from the category of the obscure and all-inclusive "allergic diseases" of Klinge, by demonstrating that neither fibrinoid degeneration nor necrotizing arteritis are exclusively the products of hypersensitivity and that caution must be exercised in interpreting these pathological pictures.

4. Finally, the demonstration that the "fibrinoid" seen in all of these diseases is not precise chemical material but refers only to a "gross" picture, conceivably due to varied chemical substances and the result of different physiologic mechanisms, has stimulated the search for the proper identification of the fibrinoid change in each disease. In all least one disease, disseminated lupus erythematosus, this sub-

stance is now believed to contain breakdown products of deoxyribose nucleic acid, the depolymerization of which is possibly controlled directly or indirectly by the L. E. serum factor of Haserick.

Dr. Paul Klemperer gave invaluable advice in the preparation of this review.

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SOME MINERAL CONSTITUENTS OF FINGERNAILS

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FOR YEARS many patients and physicians have recommended calcium ingestion because of brittle nails. Is there any scientific basis for this? It seemed wise to find out just what was the calcium and phosphorus content of nails.

In a cursory search of the literature available, the only paper bearing on the subject was that of Goldblum and his associates,[1] who have recently studied the metal content of skin, nails, and hair by spectrographic methods.

A study of nail brittleness has been carried out by Silver and Chiego,[2] but little mention of calcium is made. Many other factors were considered, such as iron metabolism, presence of fatty acids, occupation, nail lacquers, avitaminosis, systemic disease, pH of skin, and endocrine status.

It was decided to save nail clippings from the fingernails of both men and women having hard and brittle nails. Where possible, these clippings were separated by individuals. In addition to this, Dr. Pardo-Castello kindly sent me a large sample of nails pooled from a group of Cubans with various skin diseases.

Furthermore, 1,152 women under study on another problem were questioned as to brittleness of their nails. In this way, it was felt some idea as to the frequency of this problem could be determined. Actually, these figures give the women's own idea as to whether their nails were brittle or hard. Thirty-four per cent of the women stated their nails were brittle. Many of the same group also complained of dry skin. Silver and Chiego [3] reported housewives had an incidence of brittleness of 45.2%. It is interesting that in the 20 to 30-year-old group, housewives have the lowest incidence of nail brittleness of any group, including, among others, clerks, secretaries, and factory workers. It is, of course, assumed these individuals have no specific disease that might cause their nails to be brittle. They considered the utilization and elimination of iron an important factor in the causation of brittleness.

Brittleness is interpreted as any longitudinal or horizontal cracking or breaking of the nails. Hard nails are "normal" ones wherein this does not occur.

It takes some time to accumulate enough nails from one person to have a sufficient amount for analyses. There is obviously a tremendous individual variability in the rate of nail growth. My nails grew very much faster than some others

D. J. Kooyman, Ph.D., did the chemical analyses in this study.

Read at the Seventy-Third Annual Meeting of the American Dermatological Association, Lake Placid, N. Y., June 12, 1953.

and yet they were more brittle. Women's growth seemed slower than men's. However, their type of work may be a factor. A recent long-term study on one person's nail growth not only was interesting in this connection, but also reviewed the literature on the subject.[4] The writer did not mention, however, the review of Storey and Leblond,[5] who measured the rate of proliferation of epidermis and associated structures. Growth rates of nail can easily be measured. Fingernails

TABLE 1.—*Ash, Calcium, and Phosphorus Content of Fingernails*

Sample	Based on Dry Weight of Specimen		
	% Ash	% Ca.	% P.
No. 1 Brittle	0.71	0.075	0.029
No. 2 Brittle	Wet Ashed	0.068	0.043
No. 3 Brittle	Wet Ashed	0.071	0.032
No. 1 Pooled Cuban	Wet Ashed	0.138	0.088
No. 2 Pooled Cuban	Wet Ashed	0.213	0.088
No. 3 Pooled Cuban	1.13	0.150	0.040
No. 4 Pooled Cuban	0.85	0.165	0.032
No. 1 Male Hard	0.49	0.073	0.029
No. 1 Female Hard	0.62	0.075	0.025

TABLE 2.—*Ash, Calcium, and Phosphorus Content of Some Keratinous Tissues*

	Sample	Based on Dry Weight of Specimen		
		% Ash	% Ca.	% P.
Fingernails	Brittle (avg.)	0.71	0.071	0.035
	Hard (avg.)	0.56	0.074	0.027
	Cuban (avg.)	0.99	0.176	0.072
Human stratum corneum	No. 1 Callus	0.64	0.049	0.071
	No. 2 Callus	0.64	0.054	0.074
	No. 3 Callus	0.75	0.055	0.079
Cow Hoof	No. 1	Wet Ashed	0.140	0.082
	No. 2	0.53	0.135	0.080
	No. 3	0.77	0.135	0.069
Dog claw	No. 1 (distal)	0.78	0.006	0.026
	No. 2 (proximal)	3.4	1.09	0.45

grow faster than those of the feet. Also, nails with a broad and long matrix, such as the thumb nail, grow faster. Age is also a factor, with the rate of growth being at a maximum from 5 to 30 years.

For relationships between hard and soft keratin, an excellent review is given in a treatise on "The Growth, Replacement and Types of Hair" under the sponsorship of the New York Academy of Sciences. Particularly is the work of Giroud and Leblond of interest. Some of the following ideas are taken from their studies.[6]

Hard keratin contains at least three times as much sulfur as soft. Present reasoning is that the disulfide bonds may act as cross links between neighboring

parallel polypeptide chains to form the lattice of the keratins and thus insure their strength. Many more cystine radicals are present in hard than in soft keratin to form these cross links. All keratin structures have a framework of tonofibrils. These epidermal fibrils have been carefully studied by many authors. They are probably made up of polypeptide chains and consist of twisted protofibrils in a rope-like arrangement. Their presence in hair and nails welds the material together in a closely knit mass. It is one of the mechanisms by which the strength and chemical inertness of keratin may be explained. The difference in lipid content may also be a factor. Staining with Sudan III demonstrated a marked decrease in lipid in hard as compared with soft keratin.

Much study has been done of hair, but very little or none of nails. There are many examples of hard keratin in nature and a few of these have been studied.

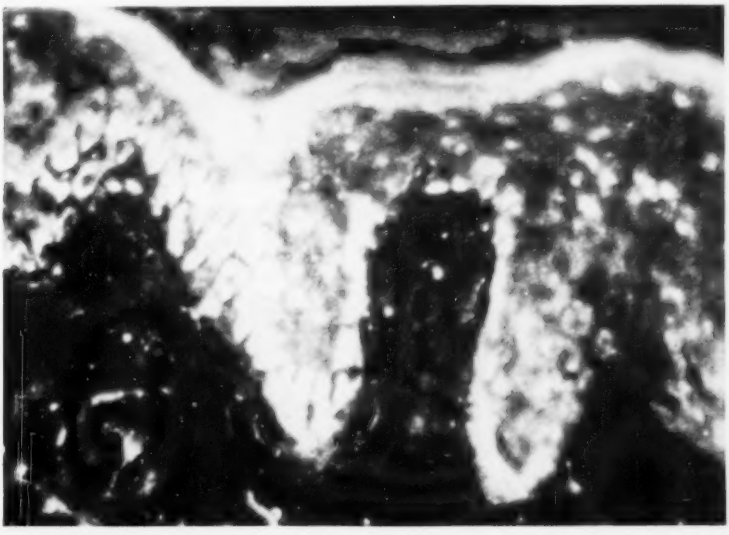

Fig. 1.—Section of microincinerated human epidermis. Note concentration of minerals in the horny and basal layers.

Common examples are horn, hoof, hedgehog quills, claws, and fish scales. Their structure is similar to, if not the same as, nails.

The presence or absence of calcium in tissue has for years been used as a criterion for the firmness or softness of protoplasm.[7] This probably stems from the hardness of bone and teeth where large quantities of calcium are present. Thus the idea may have evolved that the more calcium in the system, the harder the nails. From present knowledge of keratin development, it did not seem plausible that hard keratin might even have any such relationship.

Some concept of the distribution of the minerals in the skin and nails can be gained by examining microincinerated sections. The photographs show such an examination of skin, nail, cow hoof, and dog claw. The concentration of minerals in the epidermis is evident. This is particularly true in the cornified portions.

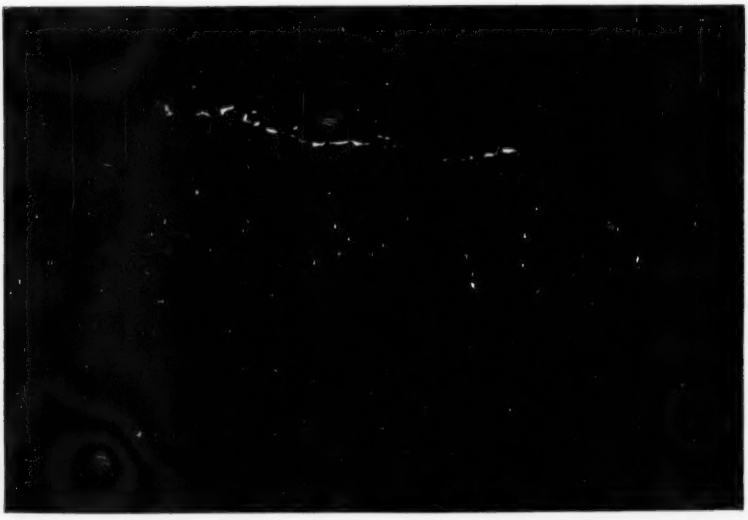

Fig. 2.—Section of microincinerated human nail cut horizontally. Small amount of minerals are concentrated at edges.

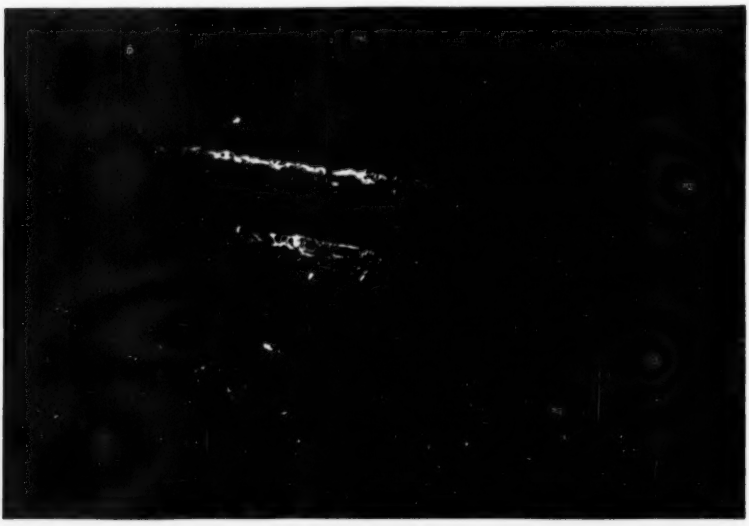

Fig. 3.—Section of microincinerated cow hoof. Small amount of minerals present is striking.

METHODS

Specimens of the keratinous tissues weighing approximately 300 mg. were washed twice by shaking vigorously in a 1% solution of Triton X-100 and rinsing 10 times with distilled water. The specimens were placed in small Petri dishes and dried in a calcium chloride desiccator for at least 72 hours.

The dried specimens were weighed and ashed in porcelain crucibles in an electric muffle furnace or digested (wet ashed) with sulfuric acid and 30% hydrogen peroxide.

The total mineral ash which remained after the dry-ashing process was weighed. It was then dissolved in several portions of dilute hydrochloric acid and made up to volume in a 25 ml. volumetric flask. The wet ashed specimens were also made up to volume in 25 ml. volumetric flasks.

Aliquots (usually 10 ml.) were used for calcium determination.

Calcium was precipitated as calcium oxalate, washed by decantation according to the method of Clark and Collip, and titrated with 0.01 N permanganate.

Phosphorus was determined by precipitating it as strychnine phosphomolybdate using Tisdall's colorimetric method.

The results of our chemical studies are summarized in the Tables.

COMMENT

The calcium and phosphorus content of nails, callus, and cow's hoof are very similar. Actually, the amount of calcium in callus may be a little lower, but not markedly so. Phosphorus, on the other hand, is higher in proportion to calcium in callus than in the other materials. It was difficult to appraise dog claw because of the presence of varying amounts of incompletely keratinized material in the matrix of the claw. This is probably the explanation for the variance in results for the two specimens.

It is interesting that the Cuban nails showed a much higher calcium content than any of the others. I have no explanation for this. They contained more pigment than any of the other specimens.

The percentage ash represents the inorganic constituents remaining after incineration. It is the nonvolatile mineral content. All organic materials, such as the proteins, were burned off in the process. This, of course, includes all nitrogen, carbon, and sulfur. In a few instances, wet ash was used, and hence no total ash values could be obtained.

The calcium and phosphorus content shows no relationship to brittleness or hardness.

There is little in the literature with which to compare these results. The mineral content of the skin has been studied by Dahn,[8] Farina,[9] and Gans.[10] For the most part the epidermis and dermis were not separated. For comparison with nail, hoof, etc., one should use only the epidermis. Cowdry and Carruthers[11] and Suntzeff and Carruthers[12] did this. They separated off the epidermis and did chemical analyses. However, they used wet weight of their specimens. This adds another variable to an already complex situation and, on account of the varying amounts of water that may be present, does not allow for comparison of figures. Their figure is 0.018 mg. per 100 cc. of calcium present in the epidermis.

Goldblum and colleagues [1] did not separate epidermis from dermis in their studies. They used a spectrographic method of analysis which has a larger variance than the quantitative chemical determinations employed in this study. These figures show larger amounts of calcium in nails than in whole skin. Inasmuch as the minerals are concentrated in the epidermis, it would seem more logical to compare its calcium content with that of nails.

Phosphorus showed little significant variation except perhaps a slight increase in relation to calcium in callus. No consistent relationship was found.

Nails are highly polymerized molecules of amino acids and may be regarded as a biological plastic.

SUMMARY

1. No consistent variation in the calcium, phosphorus, or total ash content was found among nails, callus, and cow hoof.

2. This study gave no evidence that brittleness and hardness of nails are related to their calcium or phosphorus content.

201 Auburndale Doctors Building (19).

ABSTRACT OF DISCUSSION

DR. STUART C. WAY, San Francisco: Dr. Kile's paper is an attempt to evaluate the importance of minerals in the treatment of nail brittleness. His conclusions that there was no significant variation between the calcium and phosphorus content of nails, callus, and cow's hoofs and that there was no evidence that brittleness and hardness of nails are related to the inorganic constituents in any way are extremely important because they tend to devaluate the use of calcium in certain diseases of the skin appendages. Such recognized causes of nail brittleness as detergents and cosmetics are being purposely avoided in this discussion.

A review of the literature indicates that the subject has been rather thoroughly investigated in Europe. A table taken from Hoppe, Seyler and Thierfelder showed that sulfur, an important mineral constituent, is less in cow's horn and rhinoceros horn than in the fingernail, with a still greater difference between the first two and human hair. A comparative study of the amino-acid compounds from keratins such as histidine, lysine, arginine, and cystine is likewise non-revealing in that there is apparently no relationship between the percentage present and the hardness of the substance.

Langecker gives the following analysis for the nails: water, 10.1 to 11.42%; ash, 0.32 to 1.46%; nitrogen, 14.7 to 17.0%, and sulfur, 2.47 to 3.12%. One hundred grams of nail substance contains $17.2/1000$ mg. of arsenic.

Eggleston reported that the zinc content of finger and toe nails was somewhat lower than that of head hair, averaging 196 ppm against 255 ppm for the hair. The amount of zinc found in the skin was one-eighth to one-tenth of that found in the hair, and zinc appeared to be more concentrated in the epidermis.

Klauder, who studied specimens from 44 patients with diseased and abnormal nails, found that the nails in 77.3% of this group had a lower than normal percentage of sulfur (3.2% being the average).

The relationship of the fatty acid content to nail brittleness was given consideration, although the amount present, according to Fleish, is negligible. Silver and Chiego found that the fat content of fingernails was extremely small and varied from 0.15 to 0.76%.

The water content of keratins varies from 10 to 30%, and this suggests a partial answer to our problem in that nail brittleness may in part depend upon the ability of the nail substance to absorb and hold water. In support of this is the fact that nail brittleness is more pronounced in

winter and less so in summer. Research to date leads one to conclude that factors other than their mineral constituents are responsible for nail brittleness. This conclusion is important in that it will influence future therapy.

DR. JOSEPH V. KLAUDER, Philadelphia: In consideration of the work that Brown and I did on the total sulfur content of the nails, skin and hair (ARCH. DERMAT. & SYPH. **31**:26 [Jan.] 1935; **34**:568 [Oct.] 1936) in relation to the sulfhydryl group, Dr. Kile was nice enough to discuss his paper with me. Among other things we discussed how unsatisfactory the term "brittle" is; how brittle is brittle, and how unsatisfactory it is to measure that.

I think a lay person is confused in an analogy between the hardness of bone and nails in relation to the calcium content of bone. Invariably, they ask whether they need calcium in the treatment of their brittle nails. One wonders whether the mineral content is at all concerned in what one may call brittle or soft nails. The data just presented do not suggest that it is. I think a better lead would be to search for a cement substance. I would suggest to Dr. Kile to consider that. We all know how important cement substance is in the physiology and proper functioning of different tissues. It is reasonable that brittleness of nails is concerned with loss of cement substance.

Dr. Kile is admirably situated in conducting these studies not only through Dr. Kooyman, an able chemist, but also through his access to an authority who, I think, knows more about the chemistry of skin and keratin than any one else in America or in Europe. I refer to Dr. Fred O'Flaherty, of the Tanners' Council of America in Cincinnati. He has done considerable work in relation to chemistry of animal skin. Perhaps a review of Dr. O'Flaherty's publication and contact with him might furnish some clue as to future investigation, which I hope Dr. Kile will continue.

A word about treatment. I cannot rationalize the use of gelatin in treatment of brittle nails. To my knowledge, and this is entirely extemporaneous, I do not believe that there is in gelatin any sulfur-containing amino acids. We all know that the sulfur-amino-containing acid is an important ingredient of all keratin tissue. In therapeusis of abnormal nails, the administration of a sulfhydryl compound is rationalized. An easy way of giving this is in the form of hydrolyzed wool that Brown and I proposed, liquefied wool. Hydrolyzed wool contains the important sulfo-amino compounds that are present in keratin. I am still using that preparation.

DR. V. PARDO-CASTELLO, Habana, Cuba: I have been interested in diseases of the nails for a number of years, but I never had the opportunity to contact a chemist who was willing to descend to the lower level of our chemistry of the nails. Most of them are too busy with more important affairs. I was therefore delighted to hear that Dr. Kile was successful in finding a collaborator with chemical knowledge to start this study of the chemistry of the nails.

I cannot account for the difference in the calcium content between the specimens sent from Cuba and the specimens from Dr. Kile's surroundings, but perhaps it could be explained by the fact that most of these people whose nails I clipped for several months, perhaps a year, were members of the working class. They all had very thick, stubby nails, and it was difficult sometimes to get enough of the nail to trim it.

On the other hand, the persons whose nails Dr. Kile clipped, his own and others, were of the brittle type to begin with and also from the professional class, people who do very little, if any, manual work.

To me, the question of brittleness of the nails is as baffling as it is to most of you, but I have come to the conclusion, by experience and not by chemical analysis, that there are two very important points to consider in brittleness of the nails: first, the fact that most of the brittle nails are found among women, to begin with, and also among men who do no manual work but who wash their hands a good many times a day or use chemicals, such as physicians, nurses, and others.

The content of lipids of the skin has been important in this connection, too, and it seems that the chemicals used in the enamels for nails for women and other solvents of lipids may also cause brittleness of the nail; that is, the skin, when washed repeatedly, when deprived of its lipids, becomes dry and scales freely. Something similar may occur with the nails. I know that Chiego and others have tried to prove that this is not so, but by practical observation, I believe we must look further into the possibility of the lack of lipids or the diminution of the normal amount of lipids causing fragilitas unguium.

With respect to the suggestion made by Dr. Klauder, I have used cysteine, which is easily dissolved, in the treatment of brittleness of the nails, and in spite of using it for several months in several subjects, did not get any results. Most of these patients were women, and, as in most cases, they refused to give up manicuring their nails and the use of enamels. If they did give up enamel, they usually cheated and used it one or more times a week, for a few hours to go to a party, but they do not give up the use of the enamel for any length of time.

Dr. Herbert S. Alden, Atlanta, Ga.: I had no intention of discussing this paper at all until Dr. Kile mentioned something about the growth of the nail. In evaluating results of treatment, the measure of the time of growth of the nail would seem to be important.

It occurred to me that a report on a manner of measuring nails that has been known for many years in the North Carolina mountains would not be amiss. There is and has been for many years a custom that when a boy is 8 years old, he is given the first female pig of the litter that is born closest to his eighth birthday. His father then tells Junior, "You are now 8, and the old sow out there is going to be put to the boar next week and you are to get the first pig." So the boy then takes a pocketknife and bores a hole at the base of his left thumbnail, because he knows that when that hole gets out to the end of his nail it is time to go look up his sow, so he will get his pig alive. That takes exactly three months and 10 days. It is a very accurate measuring device. I have tried it on my grandson on two occasions, and it works accurately.

Dr. Fred D. Weidman, Philadelphia: The role of calcium in the brittleness appears to have been eliminated, according to both the presenter and the discussion. May I suggest one other possibility; namely, the development of parakeratosis instead of the kind of keratosis that the histologist calls hyperkeratosis. Parakeratotic material is the more fragile, more breakable (brittle). Consider, for example, the fine, delicate (brittle?) flakes of psoriasis; this is outstandingly the dermatitis in which the histopathologist observes parakeratosis. Conversely, the scale which overlies lichen planus is not of this brittle quality; it is a closely adherent kind and is more comparable to what we see in the normal keratin of the nails. That is, as every pathologist knows, in lichen planus the keratinous substance is of the hyperkeratotic type.

Dr. Roy L. Kile, Cincinnati: I want to thank the discussers for their kindness and assistance in presenting this paper.

The subject of nail brittleness is certainly a very popular one. Women are particularly interested in it. It is amazing to me how many women, even dermatologists' wives, have asked questions about their nails since they heardI was working on this problem. I only wish I could give you more information about it.

Obviously, this study was confined to normal and brittle nails. No attempt was made to observe pathological ones, nor was any attempt made to study effects of any therapy. No histological studies were done. As Dr. Klauder mentioned, I feel most fortunate in being able to work with as competent a chemist as Dr. Kooyman. Some of these determinations were run four and five times by Dr. Kooyman because of his inherent desire to be accurate. There is a lot more work involved than appears superficially.

I certainly feel that this is a fertile field for further work. It amazed me when I found how little had been done in the field of chemistry of nails. It would be most interesting to know, for instance, how much silicon there is in nails. From the work of Goldblum, there is some basis to believe it might be increased. The idea of nails being a biological plastic is also a fascinating one. Certainly, there is much to be done both in the field of normal and of pathological nails.

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STUDY OF NUTRITIONAL REQUIREMENTS OF TRICHOPHYTON TONSURANS

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AND
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TRICHOPHYTON tonsurans has assumed importance* because of the increasing frequency of scalp infections with this endothrix organism. The literature discloses little information on its metabolism since the report in 1887 by Verujski[3] on the influences of acidity, alkalinity, various hydrocarbons, and urea on its growth. Oyama,[4] cited by Robbins and Kavanagh,[5] found that thiamine had no effect on the fungus, but that rice polishings were stimulatory. Burkholder and

TABLE 1.—*Strains of Trichophyton Tonsurans Studied*

	Strain	Source
(1)	D-12	McCormack, Columbia, 1951
(2)	D-14	Baltimore Biological Laboratory, labeled T. sulfureum
(3)	D-33	Georg, Mex.-E-29-7, 1952
(4)	D-34	Georg, M-1253-51, 1952, a recent isolate from a case in a farm boy in Michigan—had contact with Mexican workers in beet industry
(5)	D-36	Georg, 394, 1952, strain obtained from Sabouraud's laboratory in 1929 by Dr. Benham
(6)	D-41	Conant, 2285, Dr. R. Vidal, Havana, Cuba
(7)	D-43	Conant, 2264, Dr. J. N. Patterson, Tampa, Florida
(8)	D-45	Cury, #2928, Instituto Oswaldo Cruz, Brazil
(9)	D-47	Emmons, 662, Guatemala
(10)	D-49	Emmons, A465, Baltimore
(11)	D-51	Cury, #2927, Instituto Oswaldo Cruz, Brazil
(12)	D-53	Dr. A. Kligman 2C1-Dr. Scully
(13)	D-57	Dr. A. Kligman 2C2
(14)	D-59	Dr. A. Kligman 2C7, Dr. Pipkin #11
(15)	D-61	Dr. A. Kligman 2C4, Dr. Pipkin #45

Moyer[6] stated that T. tonsurans (T. sulfureum) required thiamine but was not stimulated by the addition of liver or peptone. Drouhet and Mariat[7] recently reported that their strains of T. tonsurans required the pyrimidine fraction of thiamine, and that organic, especially amino, nitrogen was necessary for satisfactory growth.

From the Department of Medicine, Division of Dermatology, Johns Hopkins Hospital, Baltimore.

Read at the meeting of the American Dermatological Association, Lake Placid, N. Y., June 10, 1953.

This investigation was supported by the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-153.

* References 1 and 2.

The purpose of this study was to obtain information regarding the vitamin, nitrogen, and carbon requirements for T. tonsurans.

METHOD

Fifteen strains were investigated (Table 1). One strain (D-34) is reported, as there was no significant variation. The basal medium described in Table 2 was employed in Experiments A, B, and C. It was varied as noted. In Experiment D, another medium was devised, which contained: neopeptone, 10 gm. per liter as nitrogen source; agar, 20 gm. per liter, and yeast extract, 1 gm. per liter. The carbon sources were varied as noted. Sabouraud and trypticase media were employed as controls. Diameters of colonies were measured at two, four, and eight weeks and recorded as + (0.1 to 0.5 cm.); ++ (0.5 to 1.0 cm.); +++ (1.0 to 2 cm.), and ++++ (over 2 cm.).

TABLE 2.—*Basal Medium*

$MgSO_4 \cdot 7H_2O$	0.50 gm.	Trace elements as	
KH_2PO_4	0.68 gm.	H_3BO_3	28.50 γ
Na_2HPO_4	0.82 gm.	$CuSO_4 \cdot H_2O$	93.00 γ
$CaCl_2$	0.10 gm.	$H_2MoO_4 \cdot H_2O$ (85% MoO_3)	17.60 γ
Glucose	40.00 gm.	$FeNH_4(SO_4)_2 \cdot 12\ H_2O$	865.00 γ
Nitrogen	0.50 gm. except where otherwise shown	$MnSO_4 H_2O$	30.50 γ
		$ZnSO_4 \cdot 7H_2O$	395.00 γ
		Distilled water	to make 1 liter
Agar *	20.00 gm.	pH 6.8 to 7.0 adjusted colorimetrically	

* For vitamin studies agar was purified.[8]

OBSERVATIONS

Experiment A.—Effect of Vitamins

	Medium	Strain	Growth of Colony in Weeks 2	4	8
1.	Basal medium + casein hydrolysate	D-34	+	++	+++
2.	Basal medium + asparagin	D-34	+	++	++
3.	Basal medium + ammonium nitrate	D-34	+	+++	+++
4.	Basal medium + ammonium sulfate	D-34	+	++	+++
5.	Basal medium + casein hydrolysate + thiamine	D-34	+++	++++	++++
6.	Basal medium + asparagin + thiamine	D-34	++	+++	+++
7.	Basal medium + ammonium nitrate + thiamine	D-34	++	+++	+++
8.	Basal medium + ammonium sulfate + thiamine	D-34	++	+++	+++
9.	Basal medium + casein hydrolysate + yeast extract	D-34	+++	++++	++++
10.	Basal medium + asparagin + yeast extract	D-34	++	+++	+++
11.	Basal medium + ammonium nitrate + yeast extract	D-34	++	+++	+++
12.	Basal medium + ammonium sulfate + yeast extract	D-34	++	+++	+++
13.	Sabouraud's medium	D-34	+++	++++	++++
14.	Trypticase medium	D-34	+++	++++	++++
15.	Basal medium + casein hydrolysate	Mucor ramannianus	+	+	+
16.	Basal medium + casein hydrolysate + thiamine	Mucor ramannianus	+++	++++	++++

Amounts of casein hydrolysate, asparagin, ammonium nitrate, and ammonium sulfate containing 500 mg. of nitrogen per liter were added to the basal medium. Mucor ramannianus (A15), a known thiamine (thiazole fraction)-deficient organism [8] was used to check absence of thiamine in the basal medium and its presence in thiamine-enriched media. Growth, although retarded, occurred without vitamins (A1, 2, 3, 4). The addition of thiamine hydrochloride, 1,000 γ per liter, accelerated growth (A5, 6, 7, 8) and resulted in colonies approximately equal to those grown on yeast extract (A9, 10, 11, 12), indicating that thiamine is the fraction responsible for the improved growth (Figs. 1 and 3).

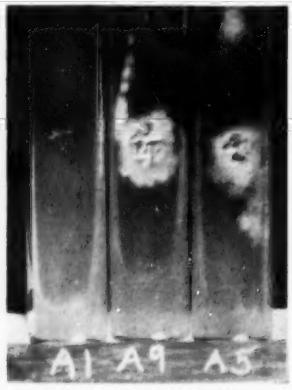

Fig. 1 (left).—Showing growth effect at six weeks of yeast extract and thiamine on purified basal medium containing casein hydrolysate as nitrogen source. *A* 1, basal medium; *A* 9, basal medium with yeast extract; *A* 5, basal medium + thiamine.

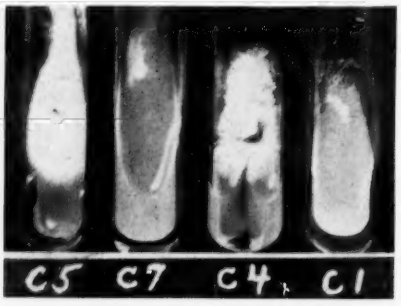

Fig. 2 (right).—Showing growth effect at four weeks of casein hydrolysate (*C* 5), hydroxyproline (*C* 7), urea (*C* 4), and potassium nitrate (*C* 1).

Experiment B.—Effects of Vitamins Plus Variation of Nitrogen Source

Medium	Strain	Growth of Colony in Weeks 2	4	8
1. Basal medium + ammonium sulfate	D-34	+	++	+++
2. Basal medium + ammonium sulfate + vitamin mixture	D-34	++	+++	+++
3. Basal medium + aspartic acid	D-34	+	++	+++
4. Basal medium + aspartic acid + vitamin mixture	D-34	++	+++	++++
5. Basal medium + casein hydrolysate	D-34	+	++	+++
6. Basal medium + casein hydrolysate + vitamin mixture	D-34	+++	++++	++++
7. Basal medium + casein + thiamine	Sordaria	+	+	+
8. Basal medium + casein + yeast extract	Sordaria	++++	++++	++++

Ammonium sulfate (B1), aspartic acid (B3), and casein hydrolysate (B5) supported retarded growth in the absence of vitamins. When 1 ml. of a stock solution of vitamins was added (B2, 4, 6), there was increased growth. (Vitamin mixture—i-inositol, 50 mg. per liter; biotin, 2 γ per liter; thiamine, 1000 γ per liter; pyridoxine, 200 γ per liter.) Sordaria, a biotin-deficient organism,[9] barely grew on thiamine-enriched medium (B7) but grew 2 cm. colonies when yeast extract was added (B8). Colonies on casein hydrolysate plus the vitamin mixture (B6) approximately equalled those on casein hydrolysate with thiamine (A5) and with yeast extract (A9). The fungus appears to be autotrophic for the other vitamins. When the nitrogen sources (A1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and B1, 2, 3, 4, 5, 6) are compared, the superiority of casein hydrolysate is apparent.

*Experiment C.—Additional Sources of Nitrogen**

Medium	Strain	Growth of Colony in Weeks 2	4	8
1. Basal medium + potassium nitrate	D-34	+	+	+
2. Basal medium + ammonium sulfate	D-34	+	+++	++++
3. Basal medium + asparagin	D-34	++	+++	+++
4. Basal medium + urea	D-34	++	+++	++++
5. Basal medium + casein hydrolysate	D-34	+++	++++	++++
6. Basal medium + hydrolized keratin	D-34	+++	++++	++++
7. Basal medium + hydroxyproline	D-34	+	+	+
8. Basal medium + casein hydrolysate + hydroxyproline	D-34	+	+	++
9. Basal medium + hydroxyproline	A. niger	++++	++++	++++
10. Sabouraud's medium	D-34	+++	++++	++++
11. Trypticase medium	D-34	+++	++++	++++

Potassium nitrate (3.6 gm. per liter), ammonium sulfate (1 gm. per liter), asparagin (2.4 gm. per liter), urea (1 gm. per liter), and hydrolized keratin (exact amount not determined) were employed separately. Urea (C4), asparagin (C3), and hydrolized keratin (C6) supported growth equal to the controls (C10, 11). With ammonium sulfate (C2), growth was initially retarded but later equalled that of urea (C4) and asparagin (C3). With potassium nitrate (C1), growth was very poor. + Colonies of 0.1 cm. in diameter or less resulted when hydroxyproline 4.7 gm. per liter was the sole nitrogen source (C7). When hydroxyproline was added to basal medium plus casein hydrolysate 20 ml. per liter, inhibition also occurred (C8). Aspergillus niger, the control organism, was not inhibited by hydroxyproline in the same concentration (C9). Figure 2 illustrates the effect of four nitrogen sources on growth.

* In this experiment basal medium contained thiamine HCl, 1 mg. per liter.

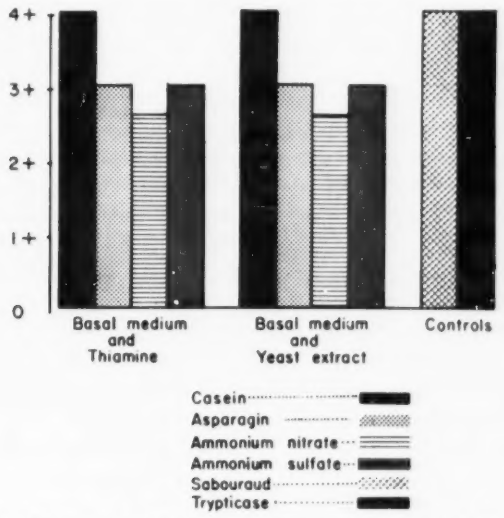

Fig. 3.—Effect of thiamine and yeast extract on growth with varied nitrogen sources.

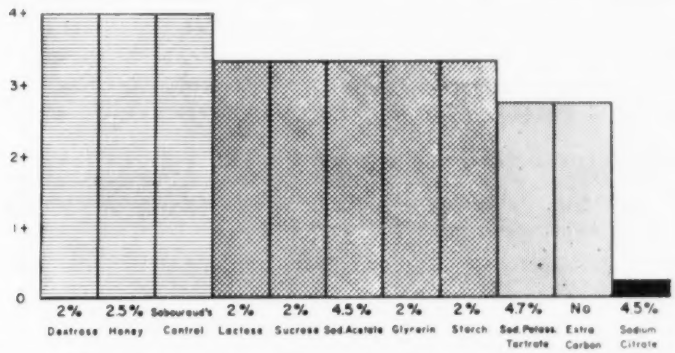

Fig. 4.—Effect of varied carbon sources on growth of Trichophyton tonsurans.

Experiment D.—Effects of Carbon Sources

	Medium	Strain	Growth of Colony in Weeks 2	4	8
1.	No carbon except that in peptone	D-34	+++	+++	+++
2.	Additional carbon as 2% glucose	D-34	+++	++++	++++
3.	Additional carbon as 2% lactose	D-34	+++	+++	+++
4.	Additional carbon as 2% sucrose	D-34	+++	+++	++++
5.	Additional carbon as 4.5% sodium acetate	D-34	+++	+++	+++
6.	Additional carbon as 2% glycerin	D-34	+++	+++	++++
7.	Additional carbon as 2% starch	D-34	+++	+++	+++
8.	Additional carbon as 2.5% honey	D-34	++++	++++	++++
9.	Additional carbon as 4.7% sodium potassium tartrate	D-34	++	++	+++
10.	Additional carbon as 3.3% sodium citrate	D-34	0	+	+
11.	Sabouraud's medium	D-34	+++	++++	++++
12.	Trypticase medium	D-34	+++	++++	++++

On honey and glucose (D2, 8) growth of ++++ colonies were observed at two weeks; with all other combinations (D1, 3, 4, 5, 6, 7, 11, 12) growth of +++ colonies were observed at two weeks, exrept on sodium potassium tartrate (D9), where there was retarded growth and on sodium citrate (D10), where there was practically no growth (Fig. 4).

COMMENT

This study, preliminary and qualitative in nature, is intended as a basis for further quantitative investigations of the metabolism of T. tonsurans. The results are in general agreement with the findings of several investigators relative to nutritional requirements of other dermatophytes.

Thiamine deficiencies have been found for other species of Trichophyton and also for Microsporum audouini.†

Insufficiency of nitrate nitrogen, suitability of ammonium and superiority of organic nitrogen have been recognized.‡ None of the 15 strains studied by us required any specific amino acid for growth, but the finding of isolates which do require some additional metabolite should occasion no surprise.§

Recent reports by Drouhet and Mariat ‖ that strains of T. tonsurans failed to utilize ammonium nitrogen are at variance with our findings. It is interesting that these workers ‖ also reported that strains of T. rubrum did not grow on ammonium nitrogen, a finding contrary to that of Silva and Benham.[16]

The apparent inhibitory action of hydroxyproline demonstrated in Experiment C is in line with previous reports ¶ on other dermatophytes. Perhaps proline can overcome this inhibition as it has been shown to do with species of Microsporum.[12]

Although glucose increased growth, it was not required as a source of energy or as structural carbon. Whether the effect of glucose was to supply additional carbon for growth or a source of energy, made available by glycolysis, we are not prepared to say.

The reason for the inhibition of growth by sodium citrate is obscure, unless one postulates an interference with the activity of arginase.[18]

CONCLUSIONS

1. T. tonsurans, while autotrophic for the other vitamins investigated, appears to be partially deficient for thiamine.

2. Organic nitrogen supports growth better than inorganic (ammonium) nitrogen.

3. Hydroxyproline inhibits growth of T. tonsurans.

4. Glucose or honey increases growth when added to a medium with a peptone as nitrogen source.

5. Sodium citrate appears to inhibit growth under experimental conditions described.

ABSTRACT OF DISCUSSION

Dr. John H. Lamb, Oklahoma City: Dr. Sullivan and his group are to be congratulated on a very concise and interesting study on the metabolism of the Trichophyton tonsurans group.

This group of fungi, as you know, is extremely resistant to treatment and in the scalp does not obey the rules of some of the other fungi with respect to disappearance at puberty. In vitro experiments by Mr. Rebell and myself in our laboratory, with several strains of Trichophyton

† References 7, 10, 13, and 14.

‡ References 10, 11, and 16.

§ References 13, 15, 16, and 17.

‖ References 7 and 15.

¶ References 10, 11, 12, and 17.

tonsurans, show this group to be inhibited by many hormones, including pregnenolone, but in vivo experiments by Dr. Pipkin are very disappointing. Several of his patients have received as high as 1 gm. per day for a period of a month without any response, in addition to 5% pregnenolone locally. However, in these chronic cases of many years' duration, I believe that a year's trial is warranted—not one or two months.

We have a small, 5-year-old girl with favus of the scalp (Trichophyton schoenleini) who has been on pregnenolone, 300 mg. daily, for over a year, and her infection has been slowly regressing. The last time she was seen, in May, 1953, she was 60% improved.

It might be that careful study as to the nitrogen and vitamin requirements in the tonsurans group may lead to some understanding as to how clinically we can control this disease. I hope so. I urge Dr. Sullivan to continue these basic metabolic studies, and I thank him again for a fine paper.

Dr. J. Walter Wilson, Los Angeles: I wish to ask Dr. Sullivan if during these studies he observed changes in the color of the gross colonies of this organism which would help to clarify the much debated question whether Trichophyton tonsurans is a single variable species of fungus or a group of species previously called by several names, such as sulfureum, epilans, sabouraudi, acuminatum cerebriforme and crateriforme.

Dr. Maurice Sullivan, Baltimore: After Pipkin published (A. M. A. Arch. Dermat. & Syph **66**:9, 1952) results of a geographic survey of the United States and emphasized the importance of Trichophyton tonsurans, we decided to study the nutritional requirements of the organism. A review of the literature disclosed only four reports on the metabolism of this important fungus. We plan a fairly comprehensive study with special attention to the amino acid requirements. Incidentally we have recently encountered our first case of Trichophyton tonsurans scalp infection in Baltimore. We expect to find more.

In answer to Dr. Wilson's questions, the experiments described in this study failed to disclose any alterations in the color of the colonies that would indicate that more than one species is involved.

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RHINOPHYMA—TREATMENT BY ELECTROSHAVING

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RHINOPHYMA is a form of rosacea due to marked hyperplasia of the sebaceous glands produced over a period of years. Marked hypertrophy of the tissues of the nose occurs. These lesions, ranging from the size of a pea to a cherry, become nodular, discolored, and lobulated. Many of the nodules and even the normal surrounding skin shows pitted scars, depressions, and enlarged follicular openings. Rosacea may still be present. The lesions may be firm or soft, and dull red to purplish in color. The cheeks and chin may also be involved. The more severe forms are usually restricted to men. Alcohol may play a part in its inception, but is a variable factor. The surface has a lowered body temperature and pales on pressure. The treatment heretofore has been by plastic surgery (scalpel or razor), excision with free skin grafting, electrosurgery, or cautery. A method is herewith presented whereby the excessive growths were removed by electroshaving (monopolar electrocutting) with excellent results.[1]

Farina [2] used the electrosurgery scalpel (bipolar) and the loop electrotome to decorticate the masses, and he concluded that in his hands surgical excision of the tumor masses with free skin grafting gave best results.

Gurdin [3] and Rosenberg [4] both reported the use of bipolar electrosurgical removal of excessive tissue in rhinophyma.

An unusually extensive case of rhinophyma was reported by Sheehan and Swanker,[5] wherein they used surgery and a full-thickness graft.

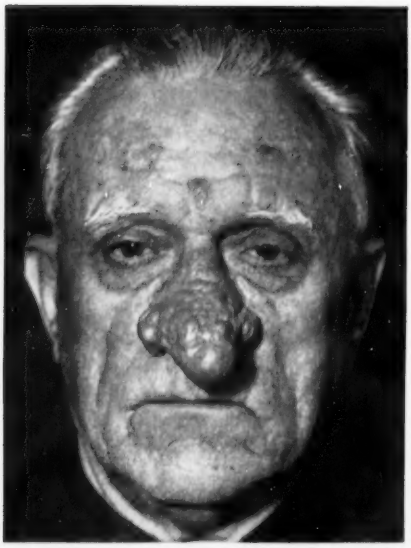
In none of the above cases was monopolar electrocutting mentioned.

REPORT OF A CASE

D. C., a man aged 63, white, born in United States. Past medical history was negative. The patient was accustomed to taking 1 or 2 oz. (29 or 59 cc.) of whiskey a day, but never in excess. The condition began about 25 years ago with small pustules on the cheeks and nose, gradually spreading to the involved area. The entire nose was deformed with marked hypertrophy (Fig. 1). The alae nasi were replaced by two cherry-sized, irregular, lobulated purplish-red to blue masses. The anterior portion of the nose extended almost to the border of the upper lip, measuring 4 cm. beyond the normal inferior nose line (Fig. 2). The anterior portion of the nose was also lobulated, broadened, and had many depressions, pits, and enlarged follicular openings from which sebum could easily be expressed. The anterior redundant tissue deviated to the left.

Presented before the Philadelphia Dermatological Society, Nov. 21, 1952.

From the Department of Dermatology and Syphilology, Temple University School of Medicine (Carroll S. Wright, M. D., Chairman), Dr. Niedelman, Associate Professor.



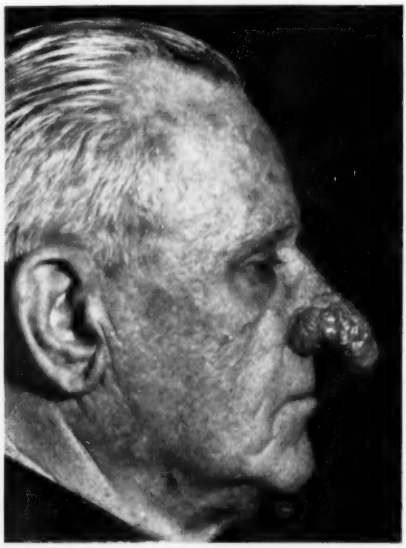


Fig. 1.—Anterior view, showing rosacea on the forehead with deformity of the nose.

Fig. 2.—Marked hypertrophy of anterior portion of nose extending downward almost to upper lip margin.

Fig. 3.—Result after electroshaving. No recurrence after one year.

PROCEDURE

The method described is an office procedure, thus enabling the patient to continue his occupation during the treatment. The method is inexpensive and bloodless, and yields cosmetic results better than or equal to plastic surgery.

After thorough cleansing of the involved area, 2% procaine hydrochloride with 1:25,000 epinephrine is injected around the nose, ringing it completely, including the upper lip and corners of the mouth. The amount is about 10 to 15 cc. This should give adequate anesthesia; if not, an infraorbital block may be done. This is accomplished by inserting a 1½ in. 22-gauge needle at each ala nasi and directing the needle upward toward the bridge of the nose into the infraorbital foramen, keeping the finger on the lower border of the orbital fossa so as not to enter the orbit. This infiltration will anesthetize the branches of the infraorbital nerve (from the maxillary nerve) as they emerge from the infraorbital foramen.

Using a monopolar, spatula-shaped, straight blade with selector switch on cutting, the procedure is carried out. This current will give both a cutting and a coagulation effect not obtained with either biterminal coagulation or electrosurgery. The areas are brushed with a current setting to produce a mild cutting effect without an intensive coagulation. This current is moderately damped and will cut and coagulate at the same time with practically no bleeding, as would occur with biterminal cutting current. The cutting should not be too deep so as not to expose bone or cartilage. The proportions of the nose and alae must be sculptured to conform to the facial configuration. There is no danger in removing the tissues within the nares and causing cicatrical stenosis. The epithelium must be protected from heat, cold, wind, or trauma until it has regenerated. The area is covered with fine-mesh, sterile, petrolatum gauze pressure bandage, which is removed in three days. After the removal of this dressing the area is left uncovered (Fig. 3).

The electroshaving method has also been used in removing fibrokeratoma of the face, dermatofibroma, and tattoos.

COMMENT

A case of rhinophyma with excellent cosmetic results treated by monopolar electroshaving is presented. This is an office procedure; infections are less likely to occur; it is inexpensive and bloodless, and it may be carried out without interference of occupation. The cosmetic results are better than or equal to plastic surgery.

2123 Pine St.

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DERMATITIS OF HOUSEWIVES AS VARIANT OF NUMMULAR ECZEMA

A Study of pH of the Skin and Alkali Neutralization by the Burckhardt Technique; Further Advances in Therapy and Prophylaxis

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A CRITICAL scrutiny of a large group of patients afflicted with occupational eczema is bound to reveal striking differences in their clinical picture. Features of contact allergic eczematous dermatitis can be readily recognized in a certain percentage of cases by the diffuse involvement of the dorsa of the hands, the presence of chemical id reactions on the flexor surface of the wrists and antecubital fossae, and the frequency of dermatitis of the face and/or swelling of the eyelids. In contrast to this picture is the appearance of the eczema in persons engaged in "wet work" or exposed to soap and cleansing agents, exhibiting a strongly alkaline reaction. Here we find that eczematous lesions appear in a patchy distribution on the hands and forearms and are not accompanied by id reactions unless there is a superimposed contact dermatitis, usually due to previous topical applications, or there is the additional factor of infection and pyogen sensitization.[1]

If we select the housewife's eczema as a representative of this group (and its high incidence becomes only too apparent in clinical and private practice), we find that the lesions vary in intensity from the dry form of eczema craquelé to a fully developed vesicular eczema in nummular patches on the dorsa of the hands and fingers. In addition, we encounter the dysidrosiform vesicular lesions on the volar surface of the fingers and on the palms. It is particularly this type of housewife's eczema which is not infrequently complicated by secondary infection. Other types of soap or alkali eczema, as seen in physicians, dentists, bartenders, and certain industrial workers, conform to this description.[2] For a long time it has been our impression that the housewife's eczema—soap dermatitis syndrome—is really nummular eczema, precipitated by the chemical action of soap and alkalis.[3] The similarities are not confined to the clinical picture, but pertain to other features

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of its nosology. To quote Jordon, Dolce, and Osborne [2] about dermatitis in housewives, the cardinal features of eczema due to soaps and allied cleansers are these:

> Most patients in whom the first attack of dermatitis appeared more than a year before they came under our observation noted that they were either completely free from the condition or improved during the warm months. . . . In most instances the dermatitis was vesicular and was confined to areas on the hands. . . . Most patients had patches on the dorsum of the hands with involvement of one or more of the fingers. . . . The eczema in many of our cases had been erroneously diagnosed as ringworm and nearly all long-standing cases had run the gamut of ringworm remedies.

The purpose of this study is to add further evidence to the concept that soap and alkali eczema is a variant of nummular eczema, calling for a diagnostic and therapeutic approach different from that for contact dermatitis.

METHODS OF LABORATORY STUDY

In 1935 Burckhardt described a technique to measure the ability of the skin to neutralize a dilute alkaline solution.[4] The test is simple, but time-consuming, and this may account for the fact that it has not become popular in this country.

The test was performed in an area not affected by the skin disease. The dorsal surface of the forearm was preferred, but if lesions were present here, the back was chosen. If a large number of hairs were present, these were cut close to the skin without scraping or injuring the skin. The pH of the skin was determined by means of a glass skin electrode and the Beckman potentiometer. The area was then cleansed with ether and the pH again determined in the same area.

The solution used was freshly prepared each testing day in the following manner: one cubic centimeter of 1 N sodium hydroxide was placed in a 100 cc. glass graduate and distilled water added up to 80 cc. To this 1/80 N solution of sodium hydroxide was added 40 mg. of powdered phenolphthalein. This was dissolved by inverting and agitating the stoppered graduate.

A rectangular glass block 2 by 3.5 by 1.5 cm. was applied to the prepared site and outlined with a skin pencil. A drop of testing solution was applied to the skin. Each drop of fluid was calculated to be approximately 0.044 cc. of 1/80 N sodium hydroxide and 1:2,000 phenolphthalein solution. The block was placed on the drop and gently rocked periodically to ensure mixing. The time taken to decolorize the solution was determined by stopwatch.

The determination was repeated 10 times in the same area. The skin was wiped with paper absorbent tissue between tests and the glass block cleaned and dried.

After the 10th determination had been completed, the pH of the skin was again determined with the glass electrode and Beckman potentiometer.

Our technique differed somewhat from that used by Burckhardt. We incorporated the phenolphthalein in the 1/80 N sodium hydroxide solution to make a concentration of 1:2,000 phenolphthalein, and used 1 drop of this colored solution from a pipette which delivered about 24 drops per cubic centimeter. Another addition in our technique was the measuring of the pH of the skin before and after the tests, which gave us an additional control over the correctness of the results. In comparative studies we found that these modifications from the original Burckhardt technique did not influence the outcome of the tests.

The cases were classified according to Burckhardt:

A. Quick neutralization: None of the 10 measurements required more than 5 minutes.

B. Intermediate neutralization: one or more measurements required over five minutes but not more than seven.

C. Slow neutralization: One or more measurements required more than seven minutes.

The results at which Burckhart arrived by his measurement of alkali neutralization were so significant that they gave impetus to extensive studies of the

mechanism of alkali neutralization.* In a more recent paper, Burckhardt [6] gives a review of these studies which can be summarized as follows:

The intact skin neutralizes alkalis primarily by the action of the amphoteric proteins of the keratin. Carbon dioxide is given off by the skin and apparently participates in the neutralization process. The quantities of carbon dioxide given off by the normal skin are small because of the presence of a barrier to diffusion. The carbon dioxide mechanism becomes significant only when the skin has been damaged by the prolonged action of an alkaline solution. Studies on pilocarpine sweating have shown that variations of sweat secretion have an influence on the neutralization.[9] Increased sweating improves alkali neutralization. Reduced sweating after atropine administration increases the neutralization time.

SELECTION OF CASES

The cases reported were divided into three groups and consisted of patients seen in the Out-Patient Department of Columbia-Presbyterian Medical Center (Vanderbilt Clinic), and sailors of the Merchant Marine and Coast Guard who were hospitalized at the United States Public Health Service Hospital at Stapleton, Staten Island.

Group I consisted of cases of (*a*) nummular eczema; (*b*) housewife's eczema; (*c*) sailor's eczema; (*d*) asteatosis and ichthyosis without eczema or with lesions other than those of nummular eczema.

In Group II were cases of allergic contact dermatitis, atopic dermatitis, and other skin conditions. Group III consisted of cases of noneczematous skin lesions, mostly benign skin tumors, and of cases of venereal disease.

The composition of Group I requires further explanation. The difficulties of separating housewife's eczema from nummular eczema became apparent again in these cases, and therefore the following criteria were used: Patients who had lesions of eczema on other parts of the body (especially on the lower extremities) in addition to or without eczema of the hands and forearms were grouped under nummular eczema. So were those patients who had nummular eczema of the hands which could not be attributed to occupational exposure. If the patient was a housewife and had lesions on the hands and forearms only, the diagnosis of housewife's eczema was made (unless the diagnosis of allergic contact dermatitis could be established). The special group of sailor's eczema was a rather artificial one. Long experience with sailors and knowledge of their occupational hazards shows that the incidence of widespread cases of nummular eczema is higher in this group than in the general population. Undoubtedly exposure to severe climatic changes and strong winds and some peculiarities in bathing and cleansing methods are among the factors accountable. If, in addition, the patient's job involved extensive use of soaps or alkalis or exposure to machine oils or kerosene, we termed the case one of sailor's eczema.

It is of interest to note that nummular eczema in these men was frequently complicated by pyogenic infections, and only after clearing of the infection phase would the true nature of the dermatosis become apparent. The necessity of hospitalizing sailors who report sick on shore facilitated careful and continuous observation and study.

* References 7 and 8. For a bibliography consult Burckhardt.[6]

RESULTS OF ALKALI NEUTRALIZATION TESTS AND pH DETERMINATIONS OF THE SKIN

Of the cases studied, 66 were sufficiently investigated and followed for this publication. Of these, 30 were in Group I, comprising cases of nummular eczema, housewife's and sailor's eczema, and asteatosis and 1 case of ichthyosis; 36 were in Groups II and III, serving as controls. More than 150 alkali neutralization tests

TABLE 1.—*Summary of Thirty Group I Cases Studied*

Sex	Identification Initials	Affected Areas	Alkali Neutralization	pH
	Nummular Eczema			
F	H. W.	Left hand	C	4.9
F	J. U.	Forearms, arms, legs	B	6.5
F	H. S.	Hands, forearms	C	5.9
F	J. C. (anemia, poor nutrition)	Hands	C	5.2
F	L. C. (soap dermatitis, hands; eczema craquelé legs)	Hands, legs	C	5.5-5.9
M	R. F.	Hands, elbows	C	5.5
F	M. O.	Hands, thighs, arms	C	4.8
M	E. B. (sailor, fireman)	Hands, arms, legs, buttocks	C	6.5
M	H. W. (chief engineer)	Hands, thighs, trunk	C	5.0
M	C. S. (Coast Guard clerk)	Left hand	C	5.5
M	C. H. (chief steward)	Ankles, legs, infect. ecz. derm. after injury	A-B	5.0
M	B. O. (electrician)	Hands, arms	C	4.5
M	W. F.	Dorsum, left hand, wrist and forearm, right ankle, trunk	C	4.8
M	O. H. (buoy tender)	Hands, feet, arms, legs, back	C	6.0
M	F. O'N.	Legs, arms	C	5.0
M	A. F.	Dorsum of foot and asteatosis	C	5.1
	Housewife's Eczema			
F	B. S.	Hands	C	5.7
F	L. D.	Hands	C	5.8
F	B. P.	Hands	C	5.9
F	J. F.	Hands	C	5.6
F	D. H.	Hands	C	5.5
F	B. K.	Hands	C	5.6
	Sailor's Eczema			
M	E. J. (oiler)	Hands-ankles	C	5.0
M	M. S. (deckhand)	Hands, arms, legs	C	5.0
M	M. B. (messman)	Arms, legs, back, ears	C	5.4
	Miscellaneous			
M	P. J. (mate)	Ichthyosis	C	4.8
M	B. J. (engineer)	Asteatosis of legs & arms (penicillin urticaria)	C	5.6
M	T. C. (dining porter)	Infectious eczemat. dermatitis; autosensitization	C	5.2
M	J. L.	Asteatosis; lichen simplex of ankle	C	5.75
M	C. L. (cook)	Arthritis; senile skin	C	4.8

were performed and many hundreds of pH examinations were done on these patients. Repeated tests in some of the individual cases served to control the correctness of the findings, to study the influence of weather, sweating, and other factors on the tests, and to check on the effect of certain therapeutic measures on the alkali neutralization and pH of the skin.

We believe that the results to be presented are significant; nevertheless, we are giving a Table listing all cases studied, which permits individual scrutiny of the findings (Table 1).

The results of the alkali neutralization tests and pH determinations are charted on Table 2. It can be readily seen that not one of the 30 cases in Group I had a normal alkali neutralization time (Type A); only 2 were of Type B, and 28 were of the slow alkali-neutralizing type, Type C. In the control group of 36 cases belonging to Group II and Group III, 27 showed normal (Type A) alkali neutralization; 8 were of the intermediate type, and 1 of Type C. These findings indicate that the Type C alkali neutralization is significant in the pathology and diagnosis

TABLE 2.—*Alkali Neutralization and pH of the Skin in Sixty-Six Cases of Nummular Eczema, Housewife's Eczema, Sailor's Eczema, and Controls*

Classification	No. of Cases	Alkali Neutralization			Average Highest Reading	Average pH
		A	B	C		
Group I Total	30	0	2	28	9' 13"	5.4
Nummular eczema	16	0	2	14	.....	5.4
Housewife's eczema	6	0	0	6	.....	5.7
Sailor's eczema	3	0	0	3	.....	5.1
Asteatosis	4	0	0	4	.....	...
Ichthyosis	1	..	..	1	.....	5.3
Group II Total	19	12	7	0	5' 13"	5.2
Contact-allergic eczema	10	6	4	0	.....	...
Atopic dermatitis, psoriasis, etc.	9	6	3	0	.....	...
Group III Total	17	15	1	1	3' 32"	5.2
Controls (skin tumors, venereal disease, etc.)						

TABLE 3.—*Incidence of Delayed Alkali Neutralization in Nummular Eczema and Housewife's Dermatitis Compared with That Reported by Other Authors*

	A		B		C	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Controls						
Burckhardt and others	489	54	178	22	152	19
Burckhardt (new cases)	83	63	28	21	21	16
Our cases	27	75	8	22	1	3
Alkali Eczemas						
Burckhardt and others	23	9	48	18	190	73
Burckhardt (new cases) *	6	9.5	7	11	50	75.5
Our cases	0	0	2	7	28	93

* 22 cases of mason's eczema and 41 cases of alkali-soap eczema.

of alkali eczema and nummular eczema. A comparison of our findings with those published by Burckhardt and based on his own data and those of other authors shows satisfactory conformity.

In Table 3 the comparison also shows that Burckhardt's new cases present a more clear-cut distribution of A and C types of alkali neutralization than do the total figures. Our findings at first glance seem almost too favorable in comparison, but this can be explained by the type of eczema studied by us. The predominance of nummular eczema and soap eczema in our group contrasts with the European cases, which deal primarily with occupational dermatitis and include mason's eczema.

If we summarize our own results, we find that in regard to alkali neutralization, nummular eczema and dermatitis of the housewife show a preponderance of Type C reaction. A small group of cases with asteatotic skin, but without nummular eczema, and one case of ichthyosis belong in the same category. The distribution of slow alkali neutralization in our group was similar to that of the large group of alkali eczemas studied by Burckhardt and other authors. Comparison of Group I and Group II allows the deduction that impaired alkali neutralization is not a characteristic of eczematous dermatitis but is more or less confined to a group of eczemas caused by exposure to alkalis or known to be exquisitely sensitive to soap and alkalis (nummular eczema).

The distribution of A, B, and C types of alkali neutralization in allergic contact dermatitis and atopic eczema does not differ fundamentally from that found in persons without eczematous dermatoses. It can also be seen that far more information can be obtained by performing the Burckhardt test than by pH determinations of the unaffected skin in this group of eczemas. This conforms fully with the findings of Klauder and Gross on the pH of patients with dermatitis of the hands.[10] The painstaking studies by these authors on the effect of alkali on the skin seem to reveal marked variations in alkali neutralization arrived at by an entirely different technique. To quote: "After hand washing lasting two minutes, the increase [of the pH]. . . gradually declines to the pH at the onset of the hand washing in a period ranging from about 45 minutes to more likely one to 1½ hours, and for some persons as long as two to 2½ hours." It is not possible to quote more from the wealth of information given by Klauder and Gross on the effect of soap and detergents on the skin. Suffice it to say that a careful reading of this classical treatise seems to stress rather than to contradict the findings to be gained by the alkali neutralization tests.

PHYSIOLOGIC AND ETIOLOGIC CONSIDERATIONS

The prevalence of slow alkali neutralization among patients with nummular eczema invites further comparisons between this disease and the dermatitis of housewives, physicians, dentists, and industrial workers. The clinical similarities have been stressed in previous publications and should not be repeated here. The importance of asteatosis (xerosis) of the skin in nummular eczema also has been pointed out before.† The degree of the clinical manifestations can be shown to vary from chapping of the hands and ankles to eczema craquelé of the extremities and finally to the coin-shaped vesicular eczema of the hands, extremities and other rarer locations. Patients with soap dermatitis reveal similar variations in morphology and frequently have an accompanying xerosis of the skin on other parts of the body. The improvement of nummular and housewife eczema in many instances during the warm weather can now be readily understood by the improvement of alkali-neutralization due to sweating. In this connection mention should be made of the interesting correlation of chapping of the normal skin with the dew point and barometric pressure of the air as demonstrated by Gaul and Underwood.[12] These authors mention a case of nummular eczema showing exacerbations coinciding with unfavorable atmospheric conditions.

† References 3 and 11.

The studies of Blank [13] of the factors which influence the water component of the stratum corneum stress the importance of diffusion of water from the underlying tissue for the maintenance of a soft and pliable stratum corneum. Blank postulates a barrier at or near the base of the stratum corneum or a very slow uniform rate of diffusion through the entire stratum corneum as an essential factor for the maintenance of proper moisture in the surface layers of the epidermis. As a result of the constant evaporation from the skin and of unfavorable atmospheric conditions, this ratio between evaporation and water diffusion can be upset. To quote: "Under the low relative humidity of winter weather and heated houses or the rapidly flowing air of windy conditions, the stratum corneum does dry out and the fissures of a chapped skin and the scaling of windburn can develop because of the brittleness of the dried stratum corneum." We have no data as yet available to correlate the variations in the alkali neutralization power of the skin with exact atmospheric measurements, but we have repeatedly observed an improvement of alkali neutralization in one and the same patient during humid weather.

Since alkali neutralization, as well as neutralization of acids,[14] by the skin appears to be primarily the function of the amphoteric amino acids of the keratin, one can readily conceive that the effect of atmospheric conditions on the moisture of the horny layer would produce variations in the neutralizing power of the skin.

That certain chemicals by producing dry and brittle skin may also make the patient more susceptible to the adverse effects of soap and alkali can be readily understood. If we can make any deductions from in vitro tests and experiments, then the nature of the action of soaps and especially detergents independent of the pH may produce changes in the keratin by liberating sulfhydryl groups.[15] It will be interesting to see whether these data can be correlated with clinical findings by the investigation indicated by Van Scott and Lyon.[15]

In a recent study of the effect of household detergents, Plüss [16] also stresses the fact that their action is chemical rather than allergenic.

Despite the fact that these in vitro studies seem to indicate that this particular chemical action of soaps and detergents is independent of the pH of the skin, we are inclined on the basis of our clinical observations to agree with Klauder and Gross,[10] who correlate the irritating effects of household detergents with the unnecessarily high pH.

It is fortunate for our national economy that despite these unfavorable influences of certain chemicals, cleansers, and occupational contacts, only a comparatively small percentage of housewives, professionals, and workers are incapacitated by alkali eczema. The taking of careful histories and clinical judgment itself raise great doubt that this "primary irritant dermatitis" is a function of a formula expressed by quantity, intensity, length of time of exposure, and disregard of protective measures. We offer the explanation that Burckhardt's "toxic hypersensitivity" is based on individual predisposition. A simple laboratory method to demonstrate it consists of measuring the impairment of neutralization of 1/80 N sodium hydroxide solution by the skin and a lowered resistance to 1/2 N sodium hydroxide. These tests may eventually become routine in the selection of workers for industries involving exposure to strong alkalis.

One of us (P. G.) ‡ pointed out the importance of nutrition and vitamin utilization in the successful management of nummular eczema. Since the function of

‡ References 3 and 11.

neutralizing alkalis has its site primarily in the normal keratin, the effect of vitamin A and other measures helping nutrition and improved cell metabolism can be better understood. Our data on the effect of vitamin A medication on alkali neutralization as measured by the Burckhardt technique are promising but not sufficient to be published.

The skepticism regarding nutritional therapy of nummular eczema is partly rooted in the concept of this condition as an infectious eczematoid dermatitis. We have no intention of denying that this group of eczemas shows a higher susceptibility to pyogen infection and pyogen sensitization than other forms of dermatitis (with the exception of dyshidrotic eczema, pompholyx, and dermatophytosis). The relation of the pH of the skin to infection originally postulated by Marchionini § and later successfully expounded by Peck and Rosenfeld [20] in the treatment of mycotic infections of the skin undoubtedly is a valid factor in the increased susceptibility of certain skin lesions to micro-organisms. As Klauder and Gross [10] could show, repeated and prolonged exposure to soaps and alkalis in certain occupations will cause pH levels of the skin above 7 in certain patients. The variations in the pH of the skin in our studies were not significant enough because the readings were made in areas which had not been washed for at least 12 hours preceding the test.

The role of pyogenic organisms in nummular eczema has again been brought into focus by Fowle and Rice [21] and it is gratifying to see that the importance of nutritional deficiencies in the causation of nummular eczema stressed by one of us (P. G.) as early as 1941 has been again demonstrated by these authors. The clinical evidence of "toxic hypersensitivity," to use Burckhardt's words, led one of us (P. G.) years ago to study the relationship of metal toxicity and nutrition. The increased toxicity of zinc for rats suffering from pantothenic acid deficiency could be demonstrated.[22] The protective action of a high protein diet or the addition of cystine to a synthetic diet could also be visualized clinically by the prevention of alopecia and cataract formation in rats subjected to chronic thallium poisoning.[23] Biologic antagonism not only is the basis of modern pharmacology but has borne important fruit in preventive toxicology (for example, dimercaprol [BAL]).

PROPHYLAXIS AND THERAPY

The concept that alkali eczema, especially the dermatitis of housewives, is a form of nummular eczema calls for a therapeutic program which recognizes the importance of normal keratinization of the skin. The findings of impaired alkali neutralization should not detract from the necessity of treating the underlying metabolic disturbance of the skin which often clinically manifests itself by evidence of xerosis. The role which vitamin A plays in keratinization lends rationale to its use in the treatment of the eczema group discussed in this paper. The synergistic action of other vitamins, the role of protein metabolism, and the importance of somatic disturbances and diseases, hormonal dysfunctions, and the effect of stress in its various ramifications must be considered in every case if satisfactory results are to be achieved.

§ References 17, 18, and 19.

Topical therapy should have the following objectives:

1. Elimination of a complicating infectious eczematous dermatitis or a superimposed contact dermatitis
2. Healing of the eczematous lesions by the most effective methods
3. Improvement of the general texture and metabolism of the skin
4. Protective measures against the specific action of soap and alkalis

Coal tar, in its various application forms, has been recognized as a valuable adjunct, and its action in nummular eczema may be based not only on its anti-eczematous effect, equally manifested in atopic dermatitis, but may be related to its keratoplastic action. The improvement of alkali neutralization by increased thickness of the horny layer produced by ultraviolet irradiation has been demonstrated.[6] Similarly, the keratoplastic effect of tar may bring about an improved tolerance for alkali by thickening the horny layer of the skin. White's formula of coal tar paste has stood the test of time, and the difficulties encountered because of the variations in the chemical composition of coal tars from different sources can be overcome by using a standardized commercial preparation.[24] The need for further chemical studies of the active as well as irritating principles of crude coal tar has been recently pointed out by Combes,[24] who advocates the use of a tar ointment with a low tar acid content for acute, vesicular dermatitis and one with a high tar acid content for psoriasis and chronic dermatoses.

Hydrocortisone acetate in ointment form has been found to be especially effective in a variety of eczematous dermatoses.[25] We have found it to be of definite value in the acute and subacute phase of nummular eczema and dermatitis of housewives, provided there was no complicating pyogenic infection. A comparison of the effectiveness of topical hydrocortisone therapy with that of conventional tar treatment of nummular eczema should be based not only on its immediate healing action, but also on the length of remission following therapy. Jagtman [26] recently proved the superiority of coal tar over other topical remedies in flexural eczema by using the paired technique of Siemens, and taking only the length of remission as a criterion.

The recognition of the infectious phase or the incidence of a pyogenic sensitization frequently calls for the use of antibiotics, especially in cases of alkali dermatitis. Systemic therapy is indicated in severer instances and the broad spectrum antibiotics are preferred because of their action on staphylococci. The majority of such cases can be managed by the use of topical antibiotics. The combinations of bacitracin with neomycin or polymyxin B sulfate owe their popularity not only to their effectiveness but also to their low sensitization index. When freshly prepared in a base combining polyethylene glycols with an oil-in-water emulsion, they produce prompt results and are free of the irritating action of petrolatum bases.

Oatmeal baths are a helpful substitute when avoidance of soap bathing is indicated by the presence of widespread nummular eczema, asteatosis, winter itch, bath dermatitis, etc.

Exposure to soap, alkalis, and detergents can be reduced by intelligent management but not sufficiently avoided by the housewife, often the mother of infants and small children requiring daily baths. She also has to depend on her own hands for most of the chores requiring the use of soap and detergents. Next to the housewife, physicians, dentists, nurses, cooks, hairdressers, bartenders and other occupations form the bulk of cases suffering from a condition ranging from chapped hands

through painful fissures to vesicular eczema. Avoidance of soap or the use of rubber gloves is in most instances impracticable or impossible. Barrier creams containing silicone are not well tolerated while eczematous lesions are present. One manufacturer states that his product "is suggested as a preventive measure. It is extremely occlusive and should not be used when the skin is acutely inflamed or infected."

For years lubricating creams and buffered solutions with a low pH have been recommended by other authors.|| The irritating effect of the preparations available, however, limited their use.

Clinical trial was started about two years ago with creams and ointments containing a buffered solution of aluminum acetate. Various modifications were made by the manufacturer, and resulted in a cream of the oil in water emulsion type, using a nonionic emulsifier and containing a buffered solution of aluminum acetate.

TABLE 4.—*Effect of Buffered Aluminum Acetate Cream on pH of Skin After Soap Washing for Ten Minutes*

	Identification Initials and Diagnosis			
	J. O. Erythroderma (Subsiding); Test Applied Middle Third Left Leg	A. J. Urticaria Due to Penicillin, Asteatosis; Test Applied Middle Third Left Leg	K. B. Contact Dermatitis, Nummular Eczema; Test Applied on Nummular Patch, Dorsum Middle Finger, Left Hand	J. O. Erythroderma; Test Applied on Left Forearm; No Lesions
Initial pH	6.3	5.5	6.9	5.45
pH after 10-minute washing with soap	Not done	6.1	Not done	6.5
pH 15 min. after applying buffered cream	5.0	4.75	5.45	5.35
pH 30 min. after applying buffered cream	5.05	5.2	5.6	....
pH 45 min. after applying buffered cream	5.15	5.6	5.9	....
pH 60 min. after applying buffered cream	5.5	5.5	6.0	5.35
pH 90 min. after applying buffered cream	5.2	....	6.1	....
pH 2 hr. after applying buffered cream	5.5	5.4	6.1	5.35
pH 5 hr. after applying buffered cream	5.7	....	6.4	....

We have used this cream for more than a year in a large number of cases seen at the clinic, at the hospital and in private practice. The fact that irritation was rarely encountered even though florid lesions of eczema were present made it possible to evaluate its therapeutic and prophylactic effect. The pH of the product, stated to be 4.2, could be confirmed by using a Beckman potentiometer.

The following experiment reported in a recent publication by Schmid[7] was performed in a group of patients:

Patients were subjected to a ten-minute washing with soap and the pH of the skin was determined. The buffered cream was then applied and the pH read at regular intervals up to two hours. It could be seen that satisfactory acidity of the skin was maintained for at least this period of time with one application of the cream, despite the rise of the pH after washing with soap, or the presence of a high pH before washing (Table 4).

The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalis is amply borne out by the

|| References 27 and 28.

experiments of Klauder and Gross [10] previously quoted. Our clinical trials in the large group of cases served to convince us of the value of and need for such a preparation. The patients suffering from nummular and housewife's eczema seen at the Vanderbilt Clinic were supplied with sufficient amounts of the buffered cream to be used frequently during the day and especially after any kind of washing or wet work. At night some of the patients used various other ointments containing tar, tar derivatives, and antibiotics, according to clinical indications. Others depended entirely on the use of the buffered cream even for night application. A few patients complained at first about a slight burning sensation immediately after application of the cream over areas affected by eczema, but were able to continue its use without further complaint. One patient found that the cream had produced an exacerbation of the eczema. A patch test had a negative result, however, and she resumed its use without adverse effect. It was interesting to observe the consistent requests of these patients, who had suffered for periods of several months to several years with eczema of the hands, for further supplies of the cream. Many of these housewives preferred this management to the use of rubber gloves. This was not due only to the inconvenience connected with the use of gloves, but was also due to the fact that they frequently experienced irritation and aggravation of the eczema after prolonged use of gloves.

It is not within the scope of this paper to give a detailed clinical report on the therapeutic results of the management of housewife's dermatitis and nummular eczema by the methods described. Its rationale appears to be demonstrated by findings reported in this paper and only personal experience of the practicing physician can convince him of the clinical value of this therapy.

SUMMARY AND CONCLUSIONS

The clinical appearance and symptomatology of housewife's eczema in many instances resembles that of so-called nummular eczema.

The technique of Burckhardt was used to study the alkali neutralization of the skin of these patients. The findings in 30 cases and 36 controls gave an unequivocal result. Nummular eczema and housewife eczema show impairment of the alkali-neutralizing power of the skin. Patients with the allergic type of contact dermatitis and atopic dermatitis and patients without eczematous eruptions showed a predominance of normal alkali neutralization.

The similarity of the clinical findings and the results of alkali neutralization tests suggest that housewife eczema and certain other types of so-called primary irritant dermatitis are variants of nummular eczema. They differ fundamentally from other forms of contact dermatitis. The difference between the nummular eczema type of reaction and the contact allergic sensitivity reaction of the skin can be correlated with the laboratory findings reported herein.

The studies of Burckhardt and others indicate that alkali neutralization is primarily the function of the amphoteric amino acids of the keratin. The maintenance of normal keratinization, therefore, is an important prerequisite to successful therapy in eczemas showing impaired alkali neutralization.

This objective should be approached by using nutritional therapy and measures devised to correct any systemic disturbances.

A cream containing a buffered solution in a water-miscible base was added to the therapeutic regimen. It proved helpful in maintaining the normal pH after washing with soap and gave satisfactory results in a prolonged clinical trial.

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The buffered cream, especially in the form of their product, Acid Mantle Creme, was supplied by Dome Chemicals Inc., who also gave technical aid.

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VESICULAR ERUPTIONS OF THE HANDS AND FEET OF DYSHIDROTIC TYPE

Clinical and Therapeutical Analysis

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VESICULAR eruptions of the hands and feet are frequent problems to the dermatologist and the general practitioner alike. Eczematous contact dermatitis and fungus infections of the hands and feet are generally well understood and will be excluded from this discussion. Even more common in our practice than these are the vesicular eruptions of the hands and feet commonly referred to as dyshidrosis, pompholyx, or cheiropompholyx.

A typical case of a vesicular eruption of the dyshidrotic type would be characterized by deep-set vesicles usually appearing in groups along the sides of the fingers or on the palms (Fig. 1). The lesions appear symmetrically and without previous erythema. The feet may be involved in a similar fashion with lesions on the dorsal surface of the great toe, sides of the toes, sides of the feet, or on the soles. Intense pruritus is often present 6 to 12 hours prior to the onset of the vesicles, and may lessen somewhat after their appearance, which is sudden. The deep-seated vesicles tend not to rupture, but undergo involution as a result of shrinkage and desiccation (Fig. 2). Some vesicles may enlarge to become bullae and occasionally they become pustules (Fig. 3).

Tilbury Fox first designated this condition dyshidrosis in 1873, and thought it was due to a dysfunction of the sweat glands. Jonathan Hutchinson, in 1876, called this condition cheiropompholyx, from the Greek meaning blister on the hands. Histologic studies * have demonstrated that the vesicles are not primarily connected with the sweat glands. Likewise, the eruption is not limited to the hands, but may also occur on the feet. Since the term dyshidrosis persists most frequently in the medical literature, we have chosen the term "vesicular eruptions of the hands and feet of the dyshidrotic type" to designate the condition under discussion.

The possible role of sweat retention in eczematous eruptions, as suggested by Herrmann and Sulzberger [4] and the frequent association of hyperhidrosis with dyshidrotic eruptions, led us to add the anticholinergic drugs to our other therapeutic agents in the treatment of these cases. The results were encouraging and we were stimulated to review and analyze a group of 145 such cases treated during the past 18 months.

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Read before the Section on Dermatology and Syphilology at the 102nd Annual Session of the American Medical Association, June 4, 1953.

* References 1 to 3.

The patients were carefully examined, special attention being paid to the intertriginous areas, and all suspicious lesions were smeared and cultured for fungi. All suspected or proved cases of fungus infections were excluded, since der-

Fig. 1.—Early lesions of a typical dyshidrotic eruption with grouped vesicles without erythema on the sides of the fingers.

Fig. 2.—Eruption of longer duration with vesicles and secondary exfoliation.

matophytid eruptions, though uncommon in our practice, are clinically indistinguishable from a dyshidrotic eruption. Patients with eczematous contact dermatitis on the hands and/or feet were similarly excluded. The eruption began with vesicular lesions without previous erythema in all patients included in this report.

The cases were evenly distributed throughout all decades of life, with some increase in the third and fourth decades as previously noted by Davidson and Birt.[5] There was a 40% greater incidence in women than in men (Table 1), or a ratio of about 4:3. Out of the 145 cases, 46%, or 67, were housewives (Table 2); 6%, or 9 cases, were in occupations with similar irritant exposures, such as nurses, beauticians, bartenders, and janitors; 48%, or 69, of the 145 cases were in essentially nonirritating occupations; 21%, or 31 cases, were in the managerial or white-collar group; 9%, or 13 cases, were general laborers in other clean occupations; 18%, or 25 cases, were students and children. We found no striking seasonal incidence (Table 3). There appeared to be a slight preponderance in the spring, but not in the hot weather, as suggested by others.† Of the 85 women, 72 had involvement of the hands only; 13 of these 85 cases involved the hands and feet. Of the 60 men,

Fig. 3.—Severe bullous eruption with secondary infection.

42 had involvement of the hands only, 17 of the hands and feet, and in only one man was the eruption localized to the feet. Although 46% of the cases were housewives, in only 32% (Table 4), or 47, out of the 145 was irritation from detergents and excessive wetting considered a major factor.

Many have contended that emotional tension was a factor in the production of dyshidrosis or cheiropompholyx. Becker and Obermayer [6] found neurocirculatory instability present in many of these patients in whom the diagnosis of fungus infection or eczematous contact dermatitis had been definitely excluded. S. W. Becker [7] speculated that nervous exhaustion might produce chemical substances at nerve endings which would in turn evoke manifestations in the skin. In this regard, it might be recalled that Goldman [8] reproduced dyshidrosis by injections of methacholine chloride (acetyl-beta-methylcholine).

† References 1, 2, 3, and 5.

From an analysis of our cases (Table 4), the vast majority resulted from either a series of frustrating circumstances or emotional conflict. Most of the patients were conscientious or were perfectionists in their habits. Even housewives with large families tended to be immaculate housekeepers. In 81% of our patients, or 118 cases, anxiety, tension, and nervous fatigue were considered major precipitating factors. In these cases, vexing situations, such as the care of invalid parents by the patient, life with an alcoholic spouse, the responsibility of both work to obtain a livelihood and the care of dependent children by a widowed patient, or working in unfavorable or frustrating surroundings, were found to form the background of

TABLE 1.—*Age and Sex Incidence*

Age	Under 21	21-30	31-40	41-50	Over 50
	27	33	39	22	24
Sex	M	F			
	60	85			

TABLE 2.—*Occupations*

	No.	Per Cent
Housewives	67	46
Nurses, beauticians, janitors, bartenders, etc.	9	6
Managerial and white-collar workers	31	21
Clean laborers	13	9
Students	25	18

TABLE 3.—*Seasonal Incidence and Sites of Involvement*
Season: None Particular; Slight Preponderance in Spring

Sites of Involvement	Male	Female
Hands only	42	72
Hands and feet	17	13
Feet only	1	0

TABLE 4.—*Major Precipitating Factors*

	No. Cases	Per Cent
Anxiety, tension, nervous fatigue	118	81
Detergents	47	32

emotional fatigue. Twenty-seven per cent, or 40, of the patients had associated functional disorders (Table 5), such as globus, migraine, colitis, duodenal ulcer, glossodynia, anxiety states, and behavior problems; 32%, or 46, had concomitant dermatoses, such as atopic eczema, seborrhea, nummular eczema, anogenital pruritus, urticaria, and alopecia areata; 43%, or 63 cases, had marked hyperhidrosis of either the palms or soles, or both.

Local therapy depended on the acuteness and severity of the eruption or the presence of a secondary infection. Continuous cool wet dressings with aluminum acetate (Burow's solution) diluted 1 part with 20 parts of water, Alibour water (solution containing zinc and copper sulfates) diluted 1:32, or plain tap water,

gave adequate relief and protection in acute and severe cases. On removal of the wet dressings, as at mealtime, the skin was immediately lubricated with liquid petrolatum (mineral oil), cottonseed oil, or white petrolatum to prevent excessive dryness. Cool soaks in plain tap water, or solutions such as 1:5,000 aqueous potassium permanganate, were used for 5 to 10 minutes several times a day in cases not as severe. Such soaks were immediately followed by 2 to 3% iodochlorhydroxyquin (Vioform) in a vanishing cream or grease base, or by white petrolatum. Ichthammol (Ichthyol) was similarly used, and in the noninfected cases, crude coal tar or tar derivatives at times were beneficial. Antibiotics such as chlortetracyline (Aureomycin) and oxytetracycline (Terramycin) were given by mouth if the secondary infection was severe, or if lymphangitis occurred. Occasionally, antibiotics such as neomycin, polymyxin, and bacitracin were used as local applications when infection was evident. Superficial x-ray therapy, especially in cases with associated hyperhi-

TABLE 5.—*Relation to Other Disease*

	No.	Per Cent
Associated functional disorders (globus, migraine, colitis, ulcer, glossodynia, anxiety states, behavior problems)	40	27
Concomitant dermatoses (atopic eczema, seborrhea, nummular eczema, urticaria, anogenital pruritus, alopecia areata)	46	32
Excessive hyperhidrosis	63	43

TABLE 6.—*Results from Therapy*

		Per Cent Followed
Excellent: healed in 2-3 wk.	66	48
Good to satisfactory: healed to minimal trouble 4-6 wk.	62	45
Unsatisfactory	10	7
Total cases followed	138	
Total cases in study	145	

drosis, was most helpful. Treatment was given in fractional dosages (i. e., 50 to 75 r) once a week, from one to several treatments. The hands were protected from soap and other common detergents during the eruption and for several weeks thereafter. To accomplish this, porous cotton gloves covered with either plastic or rubber gloves or mittens were used. Neutral detergents ‡ were allowed only when absolutely necessary. Anticholinergic drugs were used almost routinely. Of these, methantheline bromide § plain or with phenobarbital was prescribed in the majority of cases. Methantheline bromide with phenobarbital appeared to be the more effective. The dosage was adjusted to the level necessary to produce dryness of the mouth, and usually this required 50 mg. three to four times daily. Combinations of phenobarbital with belladonna or atropine were later used and were found effective in maintaining the improvement made, and in some cases sufficient as an adjunct in the initial treatment. A general discussion of etiologic factors was always included, usually at the time of the first office visit.

‡ pHisoderm, Winthrop-Stearns, Inc.; Acidolate, White Laboratories, Inc.; and Lowila, Westwood Pharmaceuticals.

§ Banthine, G. D. Searle & Company.

Summarizing our results (Table 6), 48% of our cases were free of the eruption within two or three weeks after the initiation of treatment. Another 45% were considered cured or satisfactorily controlled with minimal trouble within four to six weeks. Seven per cent of the cases were not satisfactorily controlled, and these included cases with concomitant atopic dermatitis or with uncontrollable environmental problems. Three cases illustrating the problems encountered, two of which were considered failures, are cited.

A 21-year-old housewife and mother of a year-old daughter had had recurrent atopic eczema since infancy. She disliked housework and did free-lance writing on the side. She had a marked vesicular eruption involving the sides of the fingers of both hands, but otherwise no trouble with her skin. Her hands would break out from contact with oranges, which she now carefully avoided. She had a coexistent severe vasomotor rhinitis, and was markedly allergic to dust, danders, pollens, grasses, and flowers. Asthmatic attacks followed exposure to feathers. Hives developed after eating fish. Our usual routine and avoidance, so far as possible, of the known allergens were unsuccessful. Only after a year of many interviews, strict avoidance of detergents, sedation with mephenesin ‖ and a course of intravenous injections of Piromen ¶ (a sterile, nonprotein, and nonantigenic bacterial polysaccharide prepared in a stable aqueous colloidal dispersion) was her dyshidrotic eruption satisfactorily controlled.

A 40-year-old housewife and mother of three had continued her work as a beautician. She had divorced her husband, but remarried him later. She was a nail biter and had a background of neurotic excoriations, an irritable bowel, and had suffered previously from psychoneurosis with an anxiety state. Her skin was intolerant to both oils and greases, and she was allergic to tar and iodochlorhydroxyquin. Although some relief was given by superficial x-ray therapy and bland ointments, response to our treatment was considered unsatisfactory.

A 30-year-old man, who worked as a school janitor, stated that he had never had any skin trouble until December of 1952. He then developed a vesicular eruption between his fingers and on the palms of his hands. At the time of his first examination, in February of 1953, he presented a dyshidrotic eruption and also had a seborrheic dermatitis of his face, ear canals, and scalp. His feet were normal except for a moderate hyperhidrosis. He admitted considerable anxiety about his responsibility for the school property, and sleeplessness at night, worrying about the steam boiler of the heating equipment. He never got his hands wet mopping, as he used a mop cart with a foot wringer. Sedation with phenobarbital and belladonna, ichthyol paste locally, and insight into the tension factors causing his illness produced clearing in four weeks.

COMMENT

There was a high incidence of this condition (52%) among persons exposed in their occupation to detergents and more than usual wetting of their hands. Eczematous contact dermatitis was the greatest problem in differential diagnosis. Are not some dyshidrotic eruptions simply a form of contact dermatitis without allergic reaction, and due to toxic or physical injury of the epidermis? Proper hand protection alone aided only a few, but was an adjunct necessary to benefit most of the others.

There is no doubt that identical vesicular eruptions of the palms and soles can be produced by many factors such as allergic (id) reactions to fungus or bacterial infections, food and inhalants, and absorption of damaged tissue products, as from burned or infected areas, from drugs, and from eczematous contact dermatitis. In our series, all suspected or proved cases of fungus infections were excluded. "Id"

‖ Tolserol, E. R., Squibb & Sons, New York.

¶ Travenol Laboratories, Inc., Morton Grove, Ill.

reactions, other than from fungus infections, were unusual; an occasional reaction of this nature was seen from medications such as penicillin, sulfonamides, and barbiturates.

SUMMARY AND CONCLUSION

One hundred forty-five cases of vesicular eruptions of the dyshidrotic type were studied and treated. Age, sex distribution, sites of involvement, and environmental factors were summarized. Hyperhidrosis, coexistent skin diseases, and other functional disorders were noted and correlated. From this study, we concluded that the greatest contributory factors were tension, anxiety, and nervous fatigue, and that the great majority of patients can be very satisfactorily helped by therapeutic discussions, sedation, and the anticholinergic drugs, of which methantheline appeared to be the most effective, along with proper local dermatologic therapy.

ABSTRACT OF DISCUSSION

Dr. Julius E. Ginsberg, Chicago: Most authors who have written on the subject of dyshidrosis agree that anxiety, nervous tension, hyperhidrosis of the palms and soles, and a greater incidence of the eruption in warm weather are commonly associated clinical findings. There has, however, been moderate disagreement on the histopathology of the disease since Tilbury Fox stated in his first monograph on this subject (Fox, T.: On Dyshidrosis, *Am. J. Syph. & Dermat.* **4**:107, 1873) that "the primary state of the disease is excessive secretion of sweat, and this finds a difficulty in escaping, and remains in the follicles to distend and otherwise disorder them."

Although Fox, Crocker, Pusey, Whimster, and some others believed that distended or ruptured glands bore a causal relation to the disease, the preponderance of histopathologic evidence indicates that the sweat glands play no such etiologic role.

The late R. L. Sutton presented a paper on the histopathology of pompholyx at the annual session of the American Medical Association 40 years ago this month (Sutton, R. L.: The Histopathology of Pompholyx, J. A. M. A. **61**:240, 1913) in which he presented microphotographs to support his belief that "the pathologic changes in pompholyx are confined almost wholly to the prickle cell layer. . . . The coil glands are not involved and the ducts are implicated only by accident." McLachlan and Brown (McLachlan, A. D., and Brown, W. H.: Cheiropompholyx, *Brit. J. Dermat.* **46**:475-477, 1944) found no valid evidence to support the contention that the disease is connected with sweat-gland retention, and they pointed out the histopathologic similarity of pompholyx vesicles of different etiology, and found the sweat ducts intact or pushed aside in the course of intraepidermal vesiculation. Recently, also, Wilson and Thackray (Wilson, H., and Thackray, A. C.: Sweat Ducts and the Pompholyx Vesicles, *Brit. J. Dermat.* **64**:402, 1952) did serial sections of typical lesions from seven cases of pompholyx and found no evidence that the vesicle results from sweat retention.

Careful study of the microphotographs presented in the papers of the authors named above, as well as those of Peck (Peck, S. M.: Epidermophytosis of the Feet and Epidermophytids of the Hands, Arch. Dermat. & Syph. **22**:40, 1930) and Pinkus (Pinkus, H.: The Wall of the Intra-Epidermal Part of the Sweat Duct, *J. Invest. Dermat.* **2**:175, 1939) for similar vesicular eruptions, reveals that the weight of evidence shows no participation of the sweat glands in the process of "blister" formation.

It is interesting to note that moist dressings and a "weak tarry ointment," as originally advocated by Fox (1873), still play a prominent role in the topical management of dyshidrosis. Superficial x-ray therapy has been a distinctly welcome therapeutic acid. Psychotherapeutic discussion and the internal pharmaceutic agents used have shown improvements which parallel the general advancement of our medical knowledge.

Dr. M. G. Fredricks, Duluth, Minn.: We have used anticholinergic drugs in dyshidrosis as another adjunct in keeping the patients' hands dry. Convincing them to wear combinations of white cotton gloves underneath and rubber gloves outside is still important, but frequently this protective measure is not enough.

After the excellent presentation of abnormalities of sweating by Dr. Marion Sulzberger at the Academy of Dermatology Meeting in December of 1951, we were stimulated to use methantheline bromide (Banthine) as an adjunct. Other anticholinergic drugs were also tried (Prantal methylsulfate, Schering Corporation [N, N dimethyl-4-piperidylidene-1,1-diphenyl-methane methyl sulfate]; Neotropine, Wm. R. Warner & Company, Inc. [2-di-ethylaminoethyl-α-(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride]; Bellergal, Sandoz Pharmaceuticals [a mixture of belladonna alkaloids with ergotamine tartrate and phenobarbital]; Donnatal, A. H. Robins Company, Inc. [a mixture of hyoscine sulfate, atropine sulfate, hyoscine hydrobromide, and phenobarbital]; Beplete Plus Belladonna, Wyeth, Inc. [a mixture of B complex factors with phenobarbital and belladonna]). We have been particularly pleased with the use of anticholinergic drugs, especially methantheline bromide. Some of our patients who have had recurrences, as dyshidrotic patients are well known to have, simply resumed their methantheline bromide and iodochlorhydroxyquin (Vioform) cream, and avoided detergents and water on their own initiative. We later learned that they controlled their problem without coming back to see us. We do feel that control of excessive sweating is a factor in the management of dyshidrosis, and that the anticholinergic drugs have added significantly to other good dermatologic therapy previously available.

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Clinical Notes, New Instruments and Techniques

CONTACT DERMATITIS OF HANDS, DUE TO ZINCHLORUNDESAL OINTMENT

Report of Three Cases

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Encouraged by the report of Sullivan and Bereston [1] concerning the efficacy of 5-chlorosalicylanilide in the treatment of tinea capitis, I placed three patients currently under therapy with zincundesal (Salundek *) ointment for tinea capitis under treatment with zinchlorundesal ointment (Ointment New Salundek †), which contains 5-chlorosalicylanilide. In each case, the adult in charge of rubbing the ointment into the scalp of the affected child developed a pruritic maculopapular erythematous contact dermatitis of the hands and forearms; therefore therapy with this ointment had to be discontinued. Since the children (in two out of three cases) were cleared shortly after the use of this ointment and since in all cases there was no irritation of any of the scalps, it was thought interesting to report the occurrence of the adult reactions in the hope that some sort of protective precautions might forestall other similar incidents.

REPORT OF CASES

CASE 1.—M. McK., was nursemaid to baby B. B., aged 13 months (suffering from Microsporum lanosum tinea capitis). Following the use of zincundesal ointment from April 3 to May 26, 1953, rubbed into the scalp of the child for 20 minutes three times a day, there was no irritation of the skin of the nurse. However, following the use of zinchlorundesal ointment containing 5-chlorosalicylanilide, there shortly developed a contact dermatitis of the hands and forearms, which cleared when the nurse was instructed to cease applying the ointment. Several weeks later, accidental exposure to the ointment brought severe recrudescence of the original dermatitis of the hands and forearms.

CASE 2.—C. B., was the mother of D. B., aged 5 years (a sister of baby B. B. [Case 1]) who also suffered from Microsporum lanosum tinea capitis. This woman had used zincundesal and also 50% tetrachloro-*p*-benzoquinone in a cholesterol absorption base,‡ rubbing them into the child's scalp for 30 minutes three times a day. The hands tolerated these medications well. However, on June 1, treatment was changed to zinchlorundesal ointment, which contained the 5-chlorosalicylanilide, and, on June 13, the mother's hands had developed a papular erythematous contact dermatitis. Discontinuance of the treatment brought quick subsidence of the contact dermatitis of the hands, along with clearing of the child's Tinea capitis, fortunately.

CASE 3.—B. P., was the mother of a 3-year-old girl with a granular T. gypseum infection of the scalp hair (nonfluorescing). This woman had been applying zincundesal ointment to the child's scalp, with some improvement in the condition and without any irritation of her hands. However, on May 20, when the treatment was changed to zinchlorundesal ointment, there gradually developed a contact dermatitis of the hands, and the ointment had to be discontinued.

* Salundek Ointment, manufactured by Wallace & Tiernan Products, Inc., Belleville, N. J., contains 2% undecylenic acid, 25% zinc undecylenate, and 5% salicylanilide in a carbowax base containing a wetting agent.

† Ointment New Salundek, manufactured by Wallace & Tiernan Products, Inc., contains 10% zinc undecylenate, 2% undecylenic acid, 3% salicylanilide, and 4% mono-and-di-chlorosalicylanilide in a carbowax base.

‡ Fifty per cent tetra-chloro-*p*-benzoquinone in a cholesterol absorption base, manufactured by Salem Pharmaceuticals, Box 722, Waterbury, Conn., as Keranil.

Further short therapy with 3% sulfur and 3% salicylic acid cream cleared the child's scalp in a few weeks, after which the mother made one application of the zinchlorundesal ointment for good luck. Thereupon the eruption on her hands broke out anew.

Certainly in these two last cases, the 5-chlorosalicylanilide has appeared to be quite effective in the therapy of scalp ringworm, though it was hazardous for the hands of the therapist in all three cases. Rubber gloves are clumsy, but they can be used.

It would appear from the nature of the reappearance of the dermatitis on slight exposure, that the eruption is on the basis of a sensitization. It would appear also, that, since the plain zincundesal ointment did not cause irritation, the offending irritant is the 5-chlorosalicylanilide contained in the zinchlorundesal ointment.

The contact dermatitis produced follows a distribution similar to the typical housewives' contact dermatitis of the hands caused by household irritants, and since the scalps of the children usually do not show irritation, the actual cause of the hand dermatitis may be overlooked.

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QUINACRINE (ATABRINE) IN TREATMENT OF SOLAR DERMATOSES

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During the past year we have had excellent results in treating chronic discoid lupus erythematosus with quinacrine (Atabrine) hydrochloride. As the great number of solar dermatoses begin each spring we had planned to see what effect the drug would have in these cases, since Page [1] had shown the time necessary to produce a minimum erythema dose of ultraviolet light to be increased from 6 to 24 seconds in one patient receiving quinacrine for 10 days; another patient receiving the drug for a similar time had shown an increase from 20 to 36 seconds. Page [1] felt that much of the effect of quinacrine in lupus erythematosus was due to the pigmentation of the skin decreasing the photosensitive reaction, which is recognized as a potent factor in this disease. He did note that this pigmentation did not explain the beneficial effects in systemic manifestations of the disease. Sulzberger and Bear * suggest that the effect of quinacrine may be due to its acting as an anti-infectious agent. We tend to support this opinion, since many of our patients have reported complete relief from itching and burning in lesions after 12 hours of quinacrine therapy, long before any pigmentation of the skin developed.

We started early this spring treating several patients whom we had followed on other treatment routines for several years, feeling that this would give a background for comparison.

CASE 1.—R. A. T., a male wheat rancher, aged 36, was seen first in April, 1949, with a violent hydroa aestivale involving the face, neck, and dorsal surface of the hands and arms. He gave a history of recurrent attacks of a similar eruption which had been incapacitating during the three previous summers. Physical examination, examination of the urine for porphyrins, complete blood cell count, urinalyses, blood sedimentation rate and sperm count were all within normal limits. However, following the treatment recommendations of Lain, Lamb, and others,[2]

From the private practice of Drs. A. R. Woodburne, O. S. Philpott, and J. A. Philpott Jr., and the Department of Dermatology, University of Colorado School of Medicine, Dr. O. S. Philpott, Professor.

* In editorial comment on abstract of article by Page,[1] 1951 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1951, p. 105.

we started use of testosterone, 25 mg. intramuscularly twice a week, and recommended that he wear a wide-brimmed hat and use a sun-screening agent whenever outdoors. He showed only moderate improvement and so 850 units of androgen was given intramuscular daily for two months, with very slight benefit. He had very little trouble during the winter but was seen again with a violent flare-up in February, 1950.

Since he had very indifferent success with steroid therapy we tried sodium paraaminobenzoate up to 10 gm. per day. He seemed to do better on this routine than on the steroids but still had much difficulty, including anorexia and nausea; however, he did fairly well even when the dose was reduced to 1 gm. four times a day. Early in 1951, we started large doses of desiccated liver by mouth and biweekly intramuscular injections of crude liver extract in 3 cc. doses. This seemed to help somewhat, and when 1 gm. doses of sodium paraaminobenzoate four times a day were added, he seemed to do fairly well. For various periods 200 mg. of tocopherol given three times daily was tried, with indifferent results.

In February, 1953, he was seen with an acute flare-up of his hydroa aestivale, and we decided that after such prolonged observation he would be an ideal case on which to begin our quinacrine observations. He was given 0.1 gm. three times a day for one week, twice daily for the second week, and once a day thereafter. He reported that after three days all the itching and burning had stopped. When he was seen three weeks later, he had no lesions and admitted that during the last week he had been negligent about his hat and protective cream and that he had worked outdoors all one sunny day without either and had no trouble. Therapy has been continued with 0.1 gm. of quinacrine hydrochloride daily for six weeks now, and we plan to reduce the dose further if possible. When seen early in May he had been entirely clear of eruption for some weeks.

CASE 2.—B. D., a female clerk, aged 20, had been seen with solar urticaria for several seasons. She had shown only partial response to many of the routines outlined in the report of Case 1. In March, 1953, she was started on the same routine and showed immediate response, with complete clearing in one week. She had had no quinacrine for three weeks, with no recurrence.

CASE 3.—C. L. LaF., a Spanish-American housewife, aged 55, presented urticarial patches over the cheeks and dorsal surfaces of the hands, with oozing and eczematoid patches over the tip of the nose and lower lip. This patient had had recurrent patches of this nature each spring for years. She showed the typical picture of polymorphic solar dermatitis. Quinacrine therapy was started as in Case 1, and she reported on her second visit that itching and burning had disappeared in 24 hours. At the end of the week all lesions had lost their edema, oozing had stopped, the lesions were all brown and scaling, and no new lesions had developed.

CASE 4.—C. M. S., a salesman, aged 34, who traveled by car over a large territory, had been seen since May, 1946, with urticarial lesions on the dorsal surface of the left hand and left malar eminence and firm, extremely pruritic nodules of the classical "prurigo of Hutchinson" over the rim of the left ear. This left-sided distribution is typical of patients exposed while driving cars.

This patient had had many of the routine measures described above, with indifferent success. By this time we were so enthusiastic about quinacrine hydrochloride in these cases that we sent him out on his two weeks' trip on the road with instructions to follow the quinacrine routine and use no protective measures. He reported back at the end of his trip with no lesions, all old areas showing only slight desquamation, and in entire comfort.

COMMENT

The above four cases are illustrative of the various types of solar dermatitis in which we have tried quinacrine. In all we have tried it in four cases of hydroa aestivale, six of solar urticaria, and several of the polymorphic and prurigo types. To date all patients have reponded as in the detailed cases. We have had one or two patients with nausea and one with diarrhea. In these cases use of the drug was stopped for a few days and then started at 0.05 or 0.1 gm. daily. Later we were able to increase it slowly until we obtained the effect desired. In more recent cases we have changed our routine of administration, hoping to avoid the unpleasant reactions. At present we start our patients on 0.1 gm. of quinacrine hydrochloride once a day for

one week, then twice a day for one week, then three times a day for a week; then we reverse the progression. We now have a few patients receiving 0.05 gm. daily and some 0.05 gm. every other day without flare-ups. So far no serious reactions to the drug have occurred and, by carefully following our patients, we hope to avoid any such complication.

The very prompt relief of symptoms of burning and itching, the cessation of oozing in the eczematoid patches, and decrease of edema in the urticarial lesions as illustrated in Case 3 make us feel that the effect is not due to the pigmentation of the skin, at least not initially. Probably the anti-infectious effect, some action in antagonizing adenyl compounds as suggested by Page,[1] or some other, unexplained, effect must be the mode of action of quinacrine, since pigmentation develops only after two to three weeks. We plan to try chloroquine phosphate, as suggested by Goldman,[4] but so far have not had time to note its effect. If this is equally effective, it will have as the beneficial factor the elimination of the pigmentation.

CONCLUSIONS

Quinacrine (Atabrine) hydrochloride by mouth has proved to be by far the most effective agent we have every employed in the treatment of solar dermatitis of all types.

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Correspondence

FURTHER STUDIES OF THE MOSAIC FUNGUS

To the Editor:—I was greatly interested to learn of the publication of the article "Further Studies of the Mosaic Fungus" by E. Silver Dowding (A. M. A. Arch. Dermat. & Syph. **66**:470 [Oct.] 1952). Since in the years 1947-1948 I also was working intensively on the problem of mosaic fungi (*Arch. Dermat. u. Syph.* **187**:61, 1948; **188**:104, 1949), I should like to congratulate the author on her excellent studies. A great many of the observations made by her agree with the results which I published. However, with all due respect, I am taking the liberty of making some comments on Dowding's interpretation of her results—namely, that mosaic fungi are fungous products.

Dowding writes (p. 471): "However, if it is a product of the epidermal cells of the host, one would expect to find it sometimes in skin that has not been parasitized by a fungus. Such a discovery has not been recorded. MacKee and Lewis systematically searched for the mosaic fungus in such nonmycotic lesions as psoriasis, lichen planus, pityriasis rosea, pemphigus, sunburn, and seborrhea, without success."

We were able to show that mosaic fungi can be found in nonmycotic lesions when these are localized to the palms and soles (pemphigus vulgaris, syphilitic pemphigus, psoriasis, secondary erythroderma, hyperhidrosis, and eczema). With this as a starting point we investigated 150 persons with normal skin. Mosaic fungi could be found on the plantar skin of all these persons. From each person investigated skin was always taken from the point of crossing of two diagonals, from the great and the small toe to the lateral and medial edges of the heel. Very frequently we found mosaic fungi also in healthy palms. Since we were able to demonstrate the presence of mosaic fungi in the plantar skin of 150 persons with normal skin, it must be considered proved that these structures are not fungous products but are, rather, substances of physiologic origin. Mosaic fungi are characterized by the following properties: solubility in lipids; solubility in glacial acetic acid, phenol, and alcoholic potassium hydroxide; solubility in alkalies when heated; insolubility in cold alcohol and water; melting with heat; transient coloration with concentrated sulfuric acid; failure to stain with ordinary fat and lipid stains.

According to our investigations, then, we are dealing with fatty (waxy) substances, which are formed in the course of an oxidation process in the epidermis of each person. Their appearance only in the region of the hands and feet is to be attributed to the particularly well-developed horny layer in these parts, which, through its longer developmental process, leading to a correspondingly increased thickness, provides the necessary conditions for lipid substances in the epidermis to be held at the surface of the body during the oxidation time necessary to form mosaic fungi. This view is strengthened also by the observation, among others, that in persons with healthy skin increased numbers of mosaic fungi will be found on the hands and feet if the hands and feet are not washed for a considerable length of time.

Dowding writes (p. 473): "When a hypha grows in the skin, it makes an easily distinguished channel through it. Filaments of mosaic fungus are sometimes found in the skin channel in which they were originally deposited by the hypha. *Often, however, they are not found in these channels. It would seem that they have changed their position.*" (Italics mine.)

Mosaic fungi form a very characteristic reticular tissue that is produced through the deposition of some of these materials in the intercellular spaces. Real fungous filaments, however, grow indiscriminately through the epidermis without predilection for the intercellular spaces. Now, to account for the typical network of mosaic fungi, Dowding must have recourse to the hypothesis that the fungous products have changed their positions. That such a shifting of position should continually result in the typical network formation seems to us very improbable, quite apart from the fact that a fungous infection is not the basis for formation of mosaic fungi. Dowding

This translation of Dr. Götz' letter was prepared in the office of the Editorial Supervisor of the Specialty Journals of the American Medical Association.

writes (p. 477): "When mosaic fungus and mycelium are both present in the skin, the mosaic is usually found at a slightly higher level, i. e., nearer the cover slip." This observation agrees with our own. However, while Dowding interprets it as follows (p. 477): "The hyphal excretions have drifted from the original position along the hyphae and become deposited, while they were in the mounting fluid, at a slightly higher level, taking the form of a network in conformity with the epidermal cells below it," we could explain the presence of the mosaic fungi near the stratum disjunctun on the basis of the oxidation of fatty materials in the epidermis taking place especially at that point.

If, as we have demonstrated, mosaic fungi are to be found on the feet of every person, less frequently on the hands, and if we consider further that fungous infections generally are localized on the feet, then the simultaneous presence of fungous hyphae and mosaic fungi in a potassium hydroxide preparation of a piece of epidermis is not surprising. According to our own investigations the interpretation of the mosaic fungi as secondary mycotic products is not in accord with the facts.

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Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

Samuel J. Zakon, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

Nov. 18, 1953

Infectious Myositis. Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Leonard Hoit.

History.—The patient is a 22-year-old Negro man. He was admitted to the hospital on February 9, and at that time he gave the following history. About three months previously he had developed the "flu," with a temperature of 101 F., nausea, vomiting, and cough. Two weeks after the onset of this illness, he was given an injection of penicillin, and within 24 hours muscle soreness developed. The soreness started in the thighs, then the arms, and then the back. After this he began having difficulty walking. He also had trouble in breathing because of the marked muscle soreness. He has had slight difficulty in swallowing.

Physical Examination.—There was moderate edema of the face, especially in the periorbital regions. There was an area of hyperpigmentation on the right side of the neck. There was apparent evidence of wasting, especially of the extremities, and there was marked muscle tenderness, especially of the arms.

The patient was unable to extend his arms fully above his head and was unable to sit up in bed without help. He moved his legs well but had difficulty in raising his lower extremities from the hip, with legs extended.

There was a Grade III systolic murmur, heard best at the fourth left intercostal space. It was transmitted to the aortic and pulmonic areas. The liver was palpable one fingerbreadth below the right costal margin. There was a generalized adenopathy.

Laboratory Findings.—Urinalysis was negative. Hemoglobin was 72%. Red blood cell count was 3,860,000; white blood cell count, 7,400; differential count showed neutrophiles 68%, band cells 8%, eosinophiles 2%, basophiles 1%, lymphocytes 20%, and monocytes 1%.

Serology was negative. Blood culture was negative. Agglutinations were negative. L.E. preparation of bone marrow was negative. Total serum protein was 6.8 gm. per 100 cc.; albumin, 3.3 gm. per 100 cc.; globulin, 3.5 gm. per 100 cc., and nonprotein nitrogen, 30 mg. per 100 cc. of blood. Creatinine measures 132.25 mg. per 24-hour urine specimen.

Chest x-ray revealed a "normal chest."

Biopsy of muscle three times was not diagnostic of dermatomyositis.

The patient was seen in consultation by the neurology service, and a diagnosis of infectious myositis was made. Prognosis for eventual remission was good. Corticotropin therapy was suggested.

The patient was placed on corticotropin, with complete remission of symptoms, although a weakness and brawny induration remained. The dosage was gradually lowered until he was symptom-free on 15 mg. purified corticotropin (Acthar Gel) twice a day. All attempts to lower the dosage below 30 mg. per day have resulted in exacerbation of his symptoms.

On October 11, corticotropin therapy was discontinued, and the patient was placed on 25 mg. of cortisone four times a day. In three days the patient began to experience an exacerbation of his symptoms, starting with pain and swelling in the thigh muscles and pain on swallowing.

On October 17, his dosage of cortisone was increased to 150 mg. per day (50 mg. every eight hours). His symptoms continued in a somewhat abated form.

On November 4, the patient's dosage of cortisone was increased to 200 mg. per day (50 mg. four times a day), and he became asymptomatic by November 6.

On November 12, the patient's dosage was reduced to 150 mg. of cortisone per day, and he remained symptom-free.

Collagen Disease? Raynaud's? Presented by Dr. Samuel Bluefarb and (by invitation) Dr. Leonard Hoit and Dr. A. L. Goldberg.

History.—The patient, a 35-year-old Negro man, has worked as a rug washer for the last 15 years. In 1940 he began to experience dull aching pains in the fingers and hands. These were especially bad in cold weather, when his hands seemed to turn an ashen color and the ache became more intensified. He took a calcium succinate and acetylsalicylic acid preparation (Dolcin) and several other remedies for his disturbance, but nothing seemed to help him. In the last two years he has noticed definite color changes in his hands of a cyanotic and ashen nature. These did not occur at any particular time. There has been no change in his pain.

About three months ago he experienced a sharp, hot, burning pain in the fifth finger of the left hand, which lasted for three days. The finger became very cold and cyanotic and then turned black and wrinkled. With this color change, the patient lost all sensation in this finger. After about one week the sensation began to return to the finger, and he experienced a dull burning type of pain. There has been no recurrence of this pain, but the finger has failed to heal properly.

The patient has never experienced any muscle cramps of his hands and has never had any claudication.

A biopsy performed at another clinic was reported as follows: Specimen was from fifth finger left hand. Artery: thickened; . . . muscularis intact; . . . lumen obliterated by connective tissue; . . . no inflammation. Skin: hyperkeratotic; atrophic epidermis with collagenosis of the superficial dermis; mild lymphocytic infiltration about the adnexal structures; patchy loss of striation of the muscle.

The past history and the family history were negative.

Differential blood cell count showed 49% polymorphonuclear cells, 2% band cells, 3% eosinophiles, 2% basophiles, 26% lymphocytes, and 18% monocytes.

X-ray studies of bone showed some loss of bone substance in the radial head.

Bone marrow showed compensated infection.

Scleroderma. Presented by Dr. David Omens and (by invitation) Dr. Harold Omens and Dr. Leonard Hoit.

About eight years ago, the patient, a 25-year-old Negro woman, first noticed a "tightness" and firmness of the skin of her fingers. These later became hyperpigmented. At no time did she feel any pain or pruritis. Three or four years later she developed a similar spot on her back, up near the neck. With the onset of colder weather, three months ago, she noticed an increased tightness and stiffness of the fingers. Soon after the onset of the back lesion she developed episodes of cold, painful, and blanched fingers, without any apparent etiology. Her only other symptom seems to be a slight but progressive weakness and tiredness.

The past history is negative. The family history is noncontributory.

Urinalysis was negative. Results of serology studies were doubtful, with the following results: nonprotein nitrogen was 30 mg. per 100 cc.; gamma globulin, 4.3 gm.; cephalin flocculation, 3+; thymol turbidity, 10.2 units; cholesterol, 105 mg.; total protein 9.6 gm.; albumin 3.9 gm., and globulin 5.7 gm. per 100 cc.

Chest x-ray revealed a normal chest. The electrocardiogram showed a normal graph.

Biopsy: Scleroderma.

Collagen Disease? Presented by Dr. James Webster and (by invitation) Dr. Stanley Huff and Dr. Leonard Hoit.

History.—This is the second hospital admission of this 22-year-old Negro woman. In February, 1953, she was admitted for pain in the fingers; an amputation and left stellate ganglionectomy were performed.

At this time she enters with the complaints of inability to speak and severe pain in the fingers of one day's duration.

About eight years ago the patient first noticed "soreness" of the finger tips and a somewhat brawny feel to the hands and arms. The tissues around the nail began to break down and slowly eroded. Whenever the patient immersed her hands in cold water, or in cold weather, she

would experience pallor, cyanosis, numbness, a cold feeling, and a burning sensation of the fingertips. These symptoms became increasingly severe, and with these episodes the patient began to develop episodes of nausea, vomiting, dyspnea, orthopnea, and a "choking" sensation.

In February, 1953, the patient had an episode of very severe pain in the fingers and gangrene set in in the fifth finger of the left hand, terminal phalanx. She entered Cook County Hospital, and an amputation and left stellate ganglionectomy were done. Despite this treatment, the pain in the fingers remained as before, and the choking sensation became worse. Cyanosis of the fingers with chilling of the hands also continued.

One day before admission (Nov. 11, 1953) the patient became very "nervous," had a severe "choking attack," and found that she could not talk.

Physical Examination.—Examination except for the hands was negative. Past history and family history were also negative, except for two or three attacks of generalized "convulsions" in 1953. The patient also has, but did not complain of, a brawny type of edema of the face and soft edema of the periorbital area.

Laboratory Findings.—Laboratory studies revealed the following: hemoglobin 74%; red blood cell count 4,500,000; white blood cell count 5,200. Differential counts: 41% polymorphonuclear cells, 5% eosinophiles, 50% lymphocytes, and 4% monocytes. There were anisocytosis, 2+; hypochromia, 1+; polychromasia, 1+, and occasional targeting. Nonprotein nitrogen was 27 gm.; total protein, 6.8 gm.; chlorides, 102 mEq. per liter; sodium, 139 mEq. per liter; potassium, 4.1 mEq. per liter. The chest x-ray was normal.

Dermatomyositis. Presented by DR. FREDERICK D. MALKINSON (by invitation) and DR. GEORGE C. WELLS (by invitation).

History.—L. F., a 52-year-old single Filipino man, was apparently in good health until four years prior to his admission, at which time he noticed the onset of a pruritic eruption over the posterior neck. Over the next year or two, similar areas appeared over the abdomen, back, chest, flexor surfaces of the arms, anterior thighs, and face. About one year prior to admission, he noted the onset of increasing muscular weakness. It became progressively more difficult for him to sit up from the supine position, to climb stairs, and to lift heavy objects. Eight months prior to admission, he was examined at the Mayo Clinic and was found to have slight secondary anemia, and his sedimentation rate was 60 mm. in an hour. There was increased excretion of creatine and creatinine in the urine. Biopsy of the skin and the left deltoid muscle, however, was not distinctive. The diagnosis was thought to rest between acute disseminated lupus erythematosus and dermatomyositis. On admission to Billings Hospital the patient stated that he had lost approximately 25 lb. (11.3 kg.) in the past two years. His appetite remained good, however, and he had no other complaints.

Physical Examination.—Physical examination revealed a well-developed, fairly well-nourished small Filipino man of stated age who appeared mildly ill but was in no acute distress.

Examination of the skin showed large plaques of bluish erythematous, lichenoid, and slightly scaling dermatitis over the lower back and posterior neck, the face, and abdomen, the flexor surfaces of the lower arms, the knees, and the right anterior thigh. All of these areas showed sharp borders and hyperpigmentation, and some showed moderate telangiectasia. Changes were reminiscent of poikiloderma. Pitted hyperpigmented scars in zosteriform arrangement were seen on the left thorax, sequelae of herpes zoster in 1950.

There appeared to be generalized muscular weakness, most evident in the arms, shoulder girdles, and thighs. The patient was unable to arise from a supine position unassisted. No muscular tenderness was noted. The remainder of the physical examination was within normal limits.

Laboratory Findings.—Hemoglobin was 11.5 gm.; red blood cell count, 4,250,000; white blood cell count, 4,500, with 56% neutrophiles, 7% eosinophiles, 1% basophiles, 27% small lymphocytes, and 9% monocytes. Two other white cell count determinations were 5,800 and 6,700. Platelet count was 245,300; hematocrit level, 38%, and sedimentation rate, 46 mm. in an hour. Urinalysis was normal. Wassermann and Kahn tests were negative.

Blood urea nitrogen was 11 mg. per 100 cc. Creatine was 430 mg. in a 24-hour urine sample. Total protein was 7.1 gm., with 3.8 gm. albumin and 3.3 gm. globulin per 100 cc. Serum sodium

was 118 mEq per liter; serum potassium, 4.1 mEq per liter; serum chloride, 88.4 mM per liter, and serum CO_2, 25.1 mM. per liter; serum pH, 7.36, and nonfasting blood sugar, 93 mg. per 100 cc. Basal metabolic rate was —2. L.E. cell test was negative.

Chest x-ray examination showed no abnormalities, and an abdominal film was negative.

Skin biopsy revealed a histologic finding compatible with dermatomyositis but not diagnostic. A muscle biopsy showed changes consistent with dermatomyositis.

Course in the Hospital.—Initially the diagnosis was thought to be a dermatomyositis, but it was felt that Addison's disease should be ruled out. In addition to the above laboratory data, a Thorn test showed a 50% eosinophile drop over a four-hour period. Repeated determinations of the patient's serum electrolytes showed an initial rise from the lower serum chloride to 102 mM. per liter on the 10th hospital day. The serum sodium, however, remained at a level of 118 to 120 mEq. per liter on three determinations. On July 9, 1953, the patient was discharged from the hospital with a diagnosis of dermatomyositis and has received weekly injections of testosterone since that time, with moderate improvement. Laboratory data have remained essentially unchanged.

Histopathology of the Skin Biopsies.—Two biopsies, one from right thigh and one from right arm, show essentially the same changes although the changes are much more pronounced in the section from the thigh. Here there is hyperkeratosis and moderate acanthosis, with thickened granular layer. The basal layer is deeply pigmented, and there is some pigment in the upper part of the dermis, mostly within melanophores. The upper third of the dermis shows marked edema and degeneration of the collagen. The capillaries are dilated, and there is a moderate lymphocytic infiltrate around some of the capillaries in the upper third of the corium together with a number of large histiocytes.

Histopathology of the Muscle Biopsy.—Within limited fields the muscle fibers range from very atrophic to large. Swollen fibers have waxy or vacuolar degenerations, often with splitting of sarcoplasm. Striations are variably preserved. There is the usual increased nuclearity where fibers are atrophic. In addition, there is a patchy loose interstitial exudation, with dense but not compact patches near some blood vessels. Mononuclear cells preponderate, but there are scattered neutrophiles and eosinophiles and a few hemosiderin-filled histiocytes.

DISCUSSION

Dr. Francis W. Lynch, St. Paul: Case 5 at the County Hospital differs from most of the group. I accept the diagnosis of lupus erythematosus of the discoid type, though the lesions are more plaques than discs. The association with tuberculosis is an item of interest in this case. I think it is unfortunate that such strong disclaimers have been made regarding a relationship between tuberculosis and lupus erythematosus. In denying that relationship, a small group of patients in whom active tuberculosis is associated with lupus erythematosus have been ignored. I am sure that group is significant.

Case 1 with the title, infectious myositis, interests me chiefly because of the report of the muscle biopsy, namely, "not diagnostic of dermatomyositis." Not all general pathologists think they have a sufficiently clear concept of the histological changes of dermatomyositis so that a positive diagnosis can be made. I would, therefore, raise the question here that if the changes are those of myositis (nonspecific) can one not accept this as a case of dermatomyositis? I think that the other features would be acceptable.

In Case 2, it is thought that there should be study by one greatly interested in vascular disease, and that this is not a dermatologic entity but secondary atrophic change on the basis of vascular disturbance. It is not a clearcut Raynaud's disease nor a clearcut scleroderma. I have no diagnosis to offer.

Case 4 was confusing, as is a diagnosis of "collagen disease." If one accepts that term, the position in relation to those who often use the term vaguely is weakened. Even when unable to make a specific diagnosis, I would still prefer to avoid the confusing term.

In Case 6, I favor the diagnosis of dermatomyositis. Although the eruption was not classic for dermatomyositis, it was even less acceptable for lupus erythematosus.

Dr. Louis Foreman, London, England: First I wish to bring to the members of this Society very good wishes from the dermatological society of which I have the honor of being president, and from the Department of Dermatology of Guy's Hospital.

The case of the patient with dermatomyositis, that of the young Negro woman, I think we can accept as dermatomyositis. The puffiness and edema of the face, the difficulty in swallowing, and the muscle weakness I think are fairly characteristic. There is one interesting fact, that is the sequel of these cases which I have seen on two occasions, namely, sudden death from heart failure. I am not sure whether the heart muscle partakes of the general myositis, but I think it must, because the patients are found dead in bed.

The other point of interest is the association of dermatomyositis when it occurs in elderly women with carcinoma. I do not think the association, although it is comparatively uncommon, is by any means rare. I, myself, have seen six cases, and through discussion of this matter for four or five years at various meetings I have heard from other dermatologists who have had similar cases. I believe usually the carcinoma is one affecting the female sex organs, uterus, ovaries, and breasts. I have seen examples of carcinoma in those organs associated with dermatomyositis. I think when women over 55 come in with dermatomyositis, one should take care to look for carcinoma in any one of those three places. Of course, there is a vague clinical association between scleroderma, myositis, dermatomyositis and so on. I have seen examples in patients who exhibited generalized venous erythema with atrophy who developed carcinoma, patients who develop erythematosclerotic patches of skin which are difficult to differentiate from areas of lupus erythematosus, and then a full-fledged picture of dermatomyositis and carcinoma. What the association is and what the mechanism is I do not know. I think it would take up too much time to try to discuss a subject about which we know so little and which is largely a philosophical one.

Dr. Hamilton Montgomery, Rochester, Minn.: In dermatomyositis, at least in adults, one finds a parenchymatous degeneration of the muscles with hyaline, granular and vacuolar degeneration of the muscles, and invasion of the muscle bundles by lymphocytes, and at times polymorphonuclear leucocytes and eosinophiles. In scleroderma, on the other hand, there are thickening to obliterative changes in the interseptal vessels resulting in hyaline and atrophic changes in the muscle bundles, which is secondary to the sclerosis of the vessels. This doesn't always hold true in children, as I have seen a moderate degree of obliterative change in the interseptal vessels. To my mind, the two conditions can be sharply differentiated in the majority of cases and only in scleroderma does one deal with a true collagenous disease. The loose usage of the term "collagenous" diseases is just as bad as lumping atopic and contact dermatoses under the old word eczema. The original case described by Jacobi of poikiloderma was really one of poikilodermatomyositis, because in his illustrations and descriptions he referred to the atrophy of the muscle and poikiloderma-like changes; the latter may be seen not only in dermatomyositis, but in a great many other conditions, from lymphoblastoma to various inflammatory dermatoses. The muscle changes in lupus erythematosus are not as prominent as they are in dermatomyositis, according to the studies that Dr. John Madden made. In very early phases of scleroderma or dermatomyositis, the clinical pictures may be indistinguishable from the acute phase of scleredema adultorum of Buschke. In regard to Case 5 at Illinois, this was a typical picture both clinically and histologically of dermatomyositis. The patient had atrophy of the major muscles of the trunk and pelvis.

Dr. S. J. Zakon: Only one case of lupus erythematosus has been presented while Dr. Foreman is here, and I would like to ask him the present status of quinacrine (Atabrine) in the management of lupus erythematosus.

Dr. Foreman: We started to see quinacrine after Page had found it was of value in lupus erythematosus. As far as I know, his use of quinacrine was quite accidental. He was medical registrar and dermatologist at Middlesex Hospital and suggested the use of quinine for one of his patients and, probably having had some experience in the Army, switched over and used quinacrine. There is no doubt that quinacrine is of great value in fixed discoid lupus erythematosus that has resisted therapy with gold, bismuth, and arsenic, and one could expect 70 to 80% improvement in those patients. In some of them cure is established; in others there is improvement in about 70 to 80%. Most of them will improve in the first six weeks of treatment. We have continued quinacrine for a period up to a year or 15 months. I have had no particular experience with chloroquine, which you use here. It appears to be effective. It has the great advantage that it does not produce pigmentation that quinacrine produces. I think it has answered the question that some people raised—whether quinacrine protects the skin against light. That

is not true. I do not know what the toxic effects of chloroquine are, but I have seen toxic effects of quinacrine used in the treatment of lupus erythematosus, parapsoriasis, lichen planus, lichen spinulosis, stomatitis, and so on. I think that it is by no means an innocuous drug, but, on the other hand, it is one of considerable value. I will be interested to know and will ask the members here what they feel about chloroquine in the treatment of lupus erythematosus, whether they have the same feeling regarding toxic reactions.

DR. F. J. SZYMANSKI: Most of you heard Dr. Michelson's wonderful paper on lupus erythematosus two months ago. He mentioned that he was able to find hematoxylin bodies in 50% of the histologic sections from the skin of patients with systemic lupus erythematosus. Ever since these hematoxylin bodies were first described by Klemperer and his group, we have searched for them, but we have satisfied ourselves that we have never seen such cells or bodies in any skin section in the cases of acute or subacute systemic lupus erythematosus that we had an opportunity to study.

DR. CLARK W. FINNERUD: I should like to ask Dr. Rothman and members of the University of Chicago Clinics if, in the instance of Case 5 at Illinois, the patient's skin changes were considered clinically to be those of dermatomyositis. We saw this man a couple of years ago in my office, and I think Dr. Szymanski and the others will agree that at that time there was no history of muscular weakness or other symptoms suggestive of dermatomyositis. We did not perform a biopsy. It seems to me that in Orientals almost any dermatitis can become a lichenoid process. I have never seen a cutaneous picture such as this in dermatomyositis, in spite of the fact that it has been proved that the patient now has that disorder. We considered his eruption at that time a generalized lichen simplex chronicus type of neurodermatitis.

DR. LEON GOLDMAN, Cincinnati: The questions regarding the clinical results with chloroquine were answered at the last meeting. Additional observations of toxicity reveal that these are less severe than with quinacrine. Some reactions continue to be vertigo, leucopenia, difficulty in visual accommodation, and some weight loss—I repeat the mention of these reactions knowing that people now are using chloroquine in almost every type of dermatosis. I am sorry to tell you today that the results of skin assay of chloroquine which I mentioned the last time are wrong, because our colorimetric assay studies also assayed the local anesthetic used. At present, more accurate control studies are being done.

DR. S. M. BLUEFARB: Possibly our case should not be in this group of patients having collagen diseases. However, we included this patient because the lesions appeared following immersion of the hands in cold water, and the so-called Raynaud's syndrome developed. This syndrome is often associated with cryoglobulins, which may be present and complicate the clinical picture of so-called collagen diseases.

DR. STEPHEN ROTHMAN: In reply to Dr. Finnerud I would like to say that lesions resembling lichenified skin are rather common in subacute and chronic forms of dermatomyositis. They may be markedly pruritic. The "pseudolichenification" in dermatomyositis differs from lichenification of atopic dermatitis mainly by an "unnatural" violaceous color, not corresponding to any shade of arterial or venous or mixed hyperemia (see also O'Leary, P. A., and Waisman, M.: ARCH. DERMAT. & SYPH. **44**:1001, 1940).

In the case presented, the peculiar unilateral localization on the chest with sharp limitation in the midline is very unusual. I agree that often no sharp borderline can be drawn between poikiloderma vascularis of Jacobi and dermatomyositis and that possibly the two conditions are identical.

DR. THEODORE CORNBLEET: I felt that the patient in Case 4 had lupus erythematosus and believe Dr. Webster thought so too. It is interesting how many of our patients with acute forms of this disease develop mental aberrations also. They have been variously diagnosed, but mostly as having dementia praecox. The mental episodes are transitory and do not coincide necessarily with the periods of high fever and toxicity. I saw one patient who had three different periods of mental derangement, each separated from the next by fairly long intervals of clarity. Each mental episode, however, came sometime after the lupus erythematosus had flared, one time after one of the recrudescences had entirely spent itself.

In each of the three patients (Cases 4, 5, and 6), there was difficulty in swallowing. In the collagen group we think of scleroderma or dermatomyositis presenting the symptom of dys-

phagia. This may be prominently present, however, in lupus erythematosus too. We studied three cases of the latter type, with the help of consultants, but could find no cause for it. There appear to be no organic changes, and the symptom is reversible. I have seen it only in patients who were seriously ill.

DR. FREDERICK D. MALKINSON (by invitation): I would like to comment on the fact that our patient has responded remarkably well to testosterone therapy. He has received 20 weekly injections of 100 to 200 mg. of testosterone cyclopropionate intramuscularly and is still showing some improvement as regards the muscle weakness. It is interesting that the pertinent laboratory data have remained unchanged, however.

Radiodermatitis? Neurotic Excoriations vs. Papulonecrotic Tuberculid? Presented by DR. MALCOLM C. SPENCER.

DISCUSSION

DR. STEPHEN ROTHMAN: The biopsy specimen is rather superficial, and I wonder if tuberculosis can be excluded on the basis of histological findings. I still maintain that "tuberculids" should not be diagnosed unless the Mantoux test is positive down to dilutions of 1:1,000,000 or 1:100,000.

DR. ADOLPH ROSTENBERG: I rise primarily to tangle with Dr. Rothman about tuberculids. I think the whole concept of tuberculids is in need of considerable revision. I am very dubious that any of these beautiful artefactal classifications, especially when they are based on immunologic alterations, have any real validity. Dr. Rothman stated that you need a high degree of tuberculin sensitivity in order to have a tuberculid. I am not at all certain that is so. Actually, according to the views of Jadassohn and his disciples, this would not be necessary, as sarcoidosis to them is a tuberculid and it is, of course, characterized by a relative or total lack of reactivity. It to me becomes somewhat difficult to explain the tuberculids simultaneously on the existence of a tuberculin sensitivity and on the nonexistence of a sensitivity. Many years ago, in 1919, Stokes wrote an interesting article on the tuberculids and suggested that the tuberculids may be examples of a nonspecific infection developing in a tuberculous patient. I think this suggestion has much merit and should be explored.

DR. ROTHMAN: There are three entities which I think all dermatologists could accept as tuberculids, if a tuberculous focus is found and the tuberculin sensitivity is high. These entities are: papulonecrotic tuberculid, lichen scrofulosorum, and erythema induratum. I was in error when I claimed that Darier, Lewandowsky, and other authors have not classified sarcoid with tuberculids. They did, and I stand corrected by Dr. Rostenberg. But I do not believe that because of this erroneous classification the whole concept of tuberculids must be given up.

Primary Oral Histoplasmosis. Presented by DR. EDWARD A. OLIVER.

History.—This 53-year-old white man, J. N. S., was admitted to Hines surgical service on Oct. 30, 1953, with the diagnosis of squamous cell carcinoma of the hard palate, primary, as the result of biopsy findings taken and revealed at another Veterans Administration hospital. He gives a history of the development of a lesion adjacent to the left upper premolar teeth and gum beginning in June, 1953, followed by the development of similar lesions on the roof of the mouth, left, and on the gum directly behind the lower incisors beginning about one month later. He consulted two dentists in the summer of 1953, one of whom made a diagnosis of trench mouth and treated him for some two months with no success; the other told the patient that he had a malignant condition and advised hospitalization. The patient states that the lesions have been characterized by dull aching pain and tenderness and have progressively increased in size. A biopsy specimen was taken in October, 1953; the examination showed squamous cell carcinoma, primary, and the patient was referred to Hines Hospital for therapy. He has no other complaints, but he states he has lost about 10 lb. (4.5 kg.) in the last five months.

His occupation is that of a cattle farmer in Nebraska, and he states that for some three months during the early spring of 1953 he contacted a mold from moist alfalfa hay while feeding it to cattle. Past history reveals the presence of a chronic prostatitis and hemorrhoids.

Physical Examination.—On the lower lip of the left midportion there is noted a 1 cm. in diameter whitish-gray plaque which is raised on an indurated base. There is noted on the roof of the mouth covering the left half of the hard palate and extending from the left molar posteriorly to the midline anteriorly a firm granulomatous lesion with a raised rolled edge which is not friable and does not bleed upon abrasion. The lesion is painful to palpation. A tender granular area is also noticed on the gingiva immediately behind the lower incisor teeth. Ear, nose, and throat consultation including laryngoscopy has been requested but has not been performed at yet.

Laboratory Findings.—On admission, white blood cell count was 5,300, with 47% neutrophiles, 50% lymphocytes, and 13% monocytes. Red blood cell count was 4,600,000, with 14 gm. of hemoglobin per 100 cc. Total protein was 7.35 gm., with 3.91 gm. albumin and 3.44 gm. globulin,

Primary oral histoplasmosis.

per 100 cc. X-rays of the paranasal sinuses, basilar view of the skull, mandible, and chest were returned as being within the limits of normal.

Six biopsies of the lesions have been performed, all of which revealed organisms typical of Histoplasma capsulatum. A slide is presented for interpretation.

Course in the Hospital.—Approximately two weeks ago numerous extractions were performed, following which there has been a partial resolution of the lesion at the base of the extracted incisor teeth. To date treatment has been palliative while I am considering the probability of eventually giving the patient stilbamidine.

DISCUSSION

DR. LOREN W. SHAFFER, Detroit (by invitation): Dr. Amolsch, Dr. Palmer, and I (ARCH. DERMAT. & SYPH. **45**:912-916 [May] 1942) reported the first case of histoplasmosis with genital lesions in 1942. The patient had genital, oral, and rectal lesions as well as pulmonary involvement and died a short time after the diagnosis was made.

The question arises in the case presented today as to the source of the infection in the mouth. There is seemingly no evidence of systemic involvement. One would assume that this is a local implantation of the organism.

It is surprising that this disease is evidently quite prevalent, as proved by positive histoplasmin tests and x-ray findings in the chest in mass surveys. Probably, as in lymphogranuloma venereum as evidenced by the high incidence of positive Frei tests in Negro patients, we are only recognizing the severe cases. The great majority of cases of histoplasmosis must go on to spontaneous healing without serious clinical manifestations.

Since our case was reported, Dr. Arthur Curtis has reported several cases with genital lesions. His cases have not ended fatally and have gone on to healing.

DR. LEON GOLDMAN, Cincinnati: I agree with Dr. Shaffer that this disease is much commoner than we would think. In a recent study in Cincinnati of over 8,000 school children, there was a very much higher percentage of positive histoplasmin tests than positive tuberculin tests, 36% positive histoplasmin tests and 3% positive tuberculin tests. We have had some instances in our area of a familial type of infection, including animals. These fascinating epidemiologic studies are being done by Schwarz and Silverman. We have been looking for a case of primary skin type of ulceration, but we have never found one, although secondary invasive histoplasmosis of the skin has been seen.

I would like to add one word of caution about the interpretation of a biopsy without culture control. Dr. Schwarz has reported that Blastomyces can be as small in section as Histoplasma and Histoplasma can be as large as Blastomyces.

The question was asked about value of the stilbamidines. In our experience, it has not been effective in histoplasmosis. There is simply no treatment for histoplasmosis.

DR. ADOLPH ROSTENBERG: As both of the previous speakers have stated, this is probably a very common disease and we should be more aware of it than most of us are. Several have spoken about the benignity of the disease. Christy has followed children in the Well Children's Clinic, in Memphis, in whom the histoplasmin test was negative. At some period during the study several of those children converted and the test became positive. There was no apparent illness, nothing to suggest that they had been exposed to the disease. The chest which was at first clear to x-ray later showed calcified areas, indicating exposure and pathological alterations, yet there had been no outward manifestations of illness even while they were under observation.

After I saw this patient at Hines Hospital, I looked up some of the literature. It is becoming increasingly evident that histoplasmosis is a much more frequent cause of disseminated pulmonary calcifications (D.P.C.) than tuberculosis. In one study, of 104 cases with D.P.C., none reacted to tuberculin alone, 93 reacted to histoplasmin alone, and 11 reacted to both histoplasmin and tuberculin. In other studies, of 114 cases of D.P.C., 2% reacted to tuberculin alone, while 94% reacted to histoplasmin alone. It is evident that some of our older ideas on pulmonary calcification were wrong.

Histoplasmosis is of interest not only for the reason just mentioned but also because it can simulate sarcoidosis and lymphomas. It is possible that the combinations might not be entirely coincidental. Histoplasmosis is a disease affecting the reticuloendothelial system. The old name was reticuloendothelial cytomycosis. Considering that, one could speculate that the appearance of change we ordinarily regard as a lymphoma might develop in involved areas. I do not think that in light of our present knowledge anyone is able to come out with any definite answer.

Another relevant point is that many of these cases of disseminated pulmonary calcifications with negative tuberculin reactions were labeled as sarcoids. It was asserted they did not react to tuberculin because they had some degree of immunity towards the tubercle bacillus, whereas the true explanation in such cases for the lack of reactivity was the simple one that they had never met the tubercle bacillus. Lord Acton once said, "The worst use to which a theory can be put is to make men insensible of the facts."

DR. M. R. CARO: I might suggest that the histoplasmin test is not as specific as the previous speakers have indicated. In a recent article there was reported a series of 1,000 histoplasmin tests from the Isthmus of Panama in which there was a high percentage of positive reactions. The last case of histoplasmosis reported from Panama was in 1904, which indicates that the positive reactions obtained to the test were nonspecific.

DR. ROSTENBERG: In answer to Dr. Caro, if you test with histoplasmin in areas where the disease does not occur you get negative histoplasmin reactions.

Lichen Corneus Hypertrophicus (Pautrier?). Presented by DR. GEORGE C. WELLS (by invitation).

History.—The patient, H. S., is a 69-year-old man, Japanese by birth but long a resident of the United States.

The eruption appeared on the legs about 20 years ago with marked pruritis, and the condition has persisted with very little change up until now, though itching is less than formerly. He received various local applications and superficial x-ray treatments in the past without any appreciable alteration of the symptoms or signs.

Lichen corneus hypertrophicus (Pautrier?). Area after one CO_2 application.

This patient was recently in Billings Hospital, where a subtotal gastrectomy was done for benign ulcer of the lesser curvature (September, 1953), and he has made a good recovery. No other significant disease has been found.

Physical Examination.—Over the fronts and sides of both legs from knee to ankle there are numerous close-set lichenoid papules, some forming thick plaques and some running in bead-like arrangements. The papules have keratotic surfaces, and some are conical and some are warty. Much of the affected region is deeply pigmented, but there are also areas of depigmentation.

Laboratory Findings.—Biopsy was made from the left leg on Sept. 8, 1953. There was marked hyperkeratosis and moderate acanthosis, and the epithelium showed exaggerated papillary folding. Some areas showed increase of pigment in the basal layer. There was a moderate lymphocytic infiltration around the small vessels in the subpapillary corium, and in

this region elastic fibers were absent, while deeper in the dermis some clumping of elastic fibers was apparent. Neither amyloid nor mucin could be seen in sections stained with Congo red and toluidine blue.

On Nov. 16, 1953, 0.1 cc. of 1% Congo red was injected into the skin of the front of the left shin.

DISCUSSION

DR. F. J. SZYMANSKI: In the history I noticed that this man is Japanese. The skin of Orientals lichenifies quite readily. I would classify this as nothing more than lichen simplex chronicus in the skin of an Oriental.

DR. M. R. CARO: I should like to make a suggestion which is probably of no interest from the standpoint of diagnosis but which could produce some benefit. I have had experience recently with a patient having similar patches on the leg and thigh. A great deal of improvement was produced by intensive freezing with solid carbon dioxide. Pending an exact diagnosis you might do the patient some good by this treatment.

DR. HAROLD SHELLOW: In a similar case, more on the order of hypertrophic lichen planus, I had asked Dr. Senear many years ago whether there was anything that could be done to alleviate itching, and he suggested the application of sodium hydroxide stick at weekly intervals. This was followed by a dramatic relief of itching. I have since used this method successfully in other cases of this sort. I suggest that if the carbon dioxide does not work that sodium hydroxide be tried.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Let me give you a word of warning in regard to the injection of Congo red into the skin of a patient suspected of having amyloidosis. We had one woman with an area over the neck and upper back, who had amyloidosis and in whom the positive reaction persisted for 10 years, so that she couldn't wear an evening gown, because of the red stain.

Blastomycosis. Presented by DR. PAUL K. WEICHSELBAUM.

History.—This 70-year-old white man was first seen on Nov. 12, 1953. He gave a history of having cleaned a sewer three months previously. Following this he developed two pustules on the chin, which grew rapidly to their present size. He also had a flat lesion on the back of the neck and another on the dorsum of the right hand.

Laboratory Findings.—Direct smear revealed Blastomyces hominis. Biopsy examination revealed microabscesses typical of this condition.

Three x-ray treatments previously given by another physician have modified the microscopic picture somewhat.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati: As you all know, we sent a questionnaire regarding blastomycosis to almost 1600 dermatologists and some 400 chest surgeons. About 100 cases of proved blastomycosis were surveyed. Some of the features were of interest. The details will be discussed in a report to be presented later. Blastomycosis is really a North American disease. It is found all over the country, including California and Florida. Curiously, the greatest number of cases reported was in Wisconsin. There was only one which could be considered as a type of primary skin inoculation. Also, it would be of some interest that many of these patients do not die quickly; the organisms may stay in the body for a long period of time. I believe that the response to the stilbamidines is more rapid than with iodides and radiation. Some of you have asked what is the frequency of relapses, following administration of stilbamidine. I am sorry that I do not know.

DR. STEPHEN ROTHMAN: I wonder why we should assume primary pulmonary infection if the x-rays of the lungs are negative. Patients with the cutaneous form of the disease can be kept alive with iodides; patients with pulmonary infection will die in spite of such therapy.

DR. GOLDMAN: This argument has been mentioned before. As you know, I had reported previously that there is such a reaction as primary cutaneous blastomycosis. It took him some time, but Dr. Schwarz has shown me that such a reaction is rare and that for such a diagnosis there must be fulfilled the same requirements for primary inoculation types as are shown, for example, in skin tuberculosis. Inoculation blastomycosis always had the primary complex of

regional lymph glands. It is important to emphasize that there is pulmonary blastomycosis without any skin lesions. This was known for some time and was reemphasized from the results of our questionnaire to the chest surgeons. Moreover, the x-rays of the chest may be negative and the patient still have pulmonary involvement. This we observed in one of our cases at the Cincinnati General Hospital. Furthermore, even in those cases in whom initially there appears to be only a single vegetative cutaneous lesion, for example, if this persists for some time, eventually recognizable visceral lesions develop. This can be established by autopsy studies. Originally, I thought the disease became systemic from the active skin focus. We cannot always find the primary focus, but we think every patient with cutaneous blastomycosis should have chest x-ray studies, even repeated at intervals. Perhaps there are also immune mechanisms in blastomycosis which we do not know, because the patients do get well in spite of therapy. The immunobiology of blastomycosis is still a vast unknown field in spite of our experience with the "blastomycin-desensitization-iodide therapy" complex.

I am not surprised at the objections to this concept, for it took me a while to accept this also. The inoculation cases have been true cases of primary complex; for example, a doctor pricks his finger and Blastomyces produces a local lesion associated with regional glands. In how many of our usual forms of cutaneous blastomycoses do you find proved regional blastomycotic lymphadenitis?

I do not think you can judge the picture of systemic involvement by the examination of the skin and one x-ray of the chest. The question regarding the value of surgical therapy if we believe in the systemic concept is a good one. We know too little about the epidemiology. Organisms are present in the skin lesion. As the lesion spreads, increased deformity may result. We are not yet satisfied completely with our systemic therapy (complete sterilization of the skin lesion). If the patient is in good condition, we recommend plastic surgery. So, for these reasons, we advise proper excision by the experienced surgeon, since the technique is a special one, as Dr. Jean Stevenson has shown. This is combined with systemic therapy, and the patient is followed, not forgotten, after plastic surgery. From data presented, it seems that the case today is one of systemic blastomycosis.

DR. CLARK W. FINNERUD: Years ago we saw a tremendous amount of blastomycosis. The cutaneous lesions were either solitary or multiple, and the majority were not regarded as systemic infections. Those regarded as systemic infections produced symptoms referable to the organs or tissues involved, and the skin lesions consisted of subcutaneous nodules which gradually became fluctuant and finally broke down to form indolent ulcers. We routinely took x-ray pictures only of this latter group of cases. It was our experience that the former group responded favorably to arsphenamine injections along with potassium iodide by mouth and x-ray therapy and that recurrences were the exception. Those regarded as systemic cases, as here described, not uncommonly proved fatal. It apparently has been proved now that many if not most of the cases which we regarded as localized infections were, in reality, systemic ones.

DR. IRENE NEUHAUSER: Did not Dr. Wilson make the statement that he thought all cases of disseminated blastomycosis were primarily systemic?

Lupus Erythematosus with History of Tuberculosis. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. SIDNEY BARSKY and DR. LEONARD HOIT.

Lupus Erythematosus, Subacute? Dermatomyositis? Presented by DR. HERBERT RATTNER and (by invitation) DR. H. RODIN and DR. LEONARD HOIT.

Dermatitis Exfoliativa (Sawdust? Penicillin?). Presented by DR. I. MYRON FELSHER and DR. J. P. ROGAN (by invitation).

Case for Diagnosis (Lymphoblastoma? with Perifollicular Localization). Presented by DR. ROBERT E. BLOOM (by invitation) and DR. ALLAN L. LORINCZ (by invitation).

Morphea? Lichen Sclerosis et Atrophicus? Presented by DR. GEORGE C. WELLS (by invitation).

Case for Diagnosis (Amelanosis?). Presented by DR. S. J. ZAKON and (by invitation) DR. H. M. LEVIN.

Parakeratosis Variegata. Presented by DR. ALBERT H. SLEPYAN.

Lymphoma. Presented by DR. GEORGE C. WELLS (by invitation).

Tinea Capitis Caused by Trichophyton Violaceum. Presented by DR. J. M. GREENHOUSE.

Hemangiectatic Hypertrophy of the Left Upper Extremity (Parks-Weber-Klippel Syndrome). Presented by DR. ALBERT H. SLEPYAN.

News and Comment

INDEXES

This issue of the ARCHIVES appears in two parts, the second of which is the index for the preceding volume. To make the index more usable to the readers and to enable them to find information with less difficulty than has been encountered in previous volumes, the index has been broken down into three separate indexes: Title Index, Author Index, and Subject Index. The Title Index, which will take the place of the six-month Table of Contents, previously published with the index of the journals, has been prepared in such form that it can be separated from the other indexes and bound in the front of the volume. It consists of the titles of the articles arranged in alphabetical order and accompanied by the name of the author, the name of the senior author if there are more than two, the names of both authors if there are two, and the page number on which the article begins. The Author Index contains the names of all authors of articles appearing in the ARCHIVES and of the presenters of cases or papers before societies. The third index, the Subject Index, contains in alphabetical order the important subjects which have been dealt with in the volume. Individual abstracts are no longer indexed; only the categories under which they have been classified are listed. Book Notices and news items are included in this Index.

Directory of Dermatologic Societies * †

INTERNATIONAL

International Congress of Dermatology and Syphilology

Guido Meischer, Chairman, International Committee, Zurich.
Sven Hellerström, Secretary, International Committee, Stockholm.
Place: Stockholm. Time: 1957.

Pan American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Joseph J. Eller, President, 745 Fifth Ave., New York 22.
John G. Downing, Secretary, 520 Commonwealth Ave., Boston.

FOREIGN

Argentina Association of Dermatology and Syphilology

Fernando M. Noussitou, President, Av. Quintana 386, Buenos Aires.
Alfredo A. Blasi, Secretary, Neuva York 3860, Buenos Aires.
Place: Ramos Mejia Hospital. Time: Second Wednesday of each month.

The British Association of Dermatology

C. H. Whittle, President, 41, Newton Road, Cambridge.
G. B. Dowling, Secretary, 24, Wimpole St., London, W.1.
Place: Cambridge. Time: June or July, 1955.

British Association of Dermatology and Syphilology (New South Wales Branch)

R. B. Perkins, President, 141 Macquarie St., Sydney.
E. J. C. Molesworth, Secretary, 235 Macquarie St., Sydney.
Place: Royal North Shore Hospital, St. Vincent's Hospital, Sydney Hospital, Royal Alexandria Hospital for Children, and Royal Newcastle Hospital. Time: 4 p.m. on Friday, approximately every two months.

Canadian Dermatological Association

D. E. H. Cleveland, President, 603 Medical-Dental Building, Vancouver, B. C.
A. Birt, Secretary, 429 Medical Arts Building, Winnipeg, Man.
Place: Winnipeg.

Dermatological Association of Australia

L. W. Linn, President, Shell House, 170 N. Terrace, Adelaide.
J. B. Cahill, Secretary, 159 Macquarie St., Sydney.
Place: Melbourne. Time: October, 1954.

German Society of Dermatology

Oscar Gans, President, Ludwig-Rehn Str. 14, Frankfurt am Main.
Hans Schuermann, Secretary, Universität-Hautklinik, Würzburg.

Israeli Dermatological Society

A. Dostrovsky, Chairman, Hebrew University Hadassah Medical School, Jerusalem.
Felix Sagher, Secretary, Hadassah University Hospital, Jerusalem.

* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

† Dates of meetings are designated only for those societies which have specified meeting times.

New Zealand Dermatological Society

R. F. Thomas, President, A. M. P. Buildings, Queen St., Auckland.
B. H. R. Hill, Secretary, P. O. Box 61, Napier.

North of England Dermatological Society

C. W. Mackenzie, President, Grayrigg, The Horseshoe, Dringhouses, York.
G. Auckland, Secretary, 14 St. John St., Manchester 3.
Place: Manchester, Leeds, Sheffield, Liverpool, and one other town, in rotation. Time: Second Tuesday, March, April, May, June, and October.

Royal Academy of Medicine in Ireland, Section of Dermatology

P. MacCarvill, President, 8, Fitzwilliam Square, Dublin.
B. Solomons, Jr., Secretary, 42, Fitzwilliam Square, Dublin.
Place: Royal College of Physicians of Ireland.

Royal Society of Medicine, Section of Dermatology

Reginald T. Brain, President, 132, Harley St., London, W.1.
P. D. Samman, Honorary Secretary, 47a, Wimpole St., W.1, London.
Place: Royal Society of Medicine, 1 Wimpole St., London, W.1. Time: 4:00 p.m., third Thursday of each month.

Sociedad Cubana de Dermatologica y Sifilografia

Alberto Oteiza Setien, President.
Guillermo Gonzalez Peris, Secretary.

Sociedad Mexicana de Dermatologia

Francisco Hernandez Zurita, President.
Fernando Latapi, Secretary, Zacatecas 220-6, México, D. F.
Place: National School of Medicine, México, D. F. Time: 9:00 p.m., first Thursday of each month.

Schweizerische Gesellschaft für Dermatologie und Venereologie

Werner Jadassohn, Chairman, Clinique Dermatologique de l'Hôpital Cantonal, Genève, Switzerland.
Wilhelm Lutz, Secretary, Dermatologische Klinik, Bürgerspital, Basel, Switzerland.

NATIONAL

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Everett C. Fox, Chairman, 318 Medical Arts Building, Dallas 1, Texas.
J. Walter Wilson, Secretary, 3875 Wilshire Blvd., Los Angeles 5.
Place: Atlantic City, New Jersey, in 1955; Chicago, in 1956. Time: June 6-10, 1955; June 11-15, 1956.

American Academy of Dermatology and Syphilology

Fred Weidman, President, Medical Laboratory, University of Pennsylvania, Philadelphia.
James R. Webster, Acting Secretary, P. O. Box 6565, Cleveland 1.
Place: Palmer House, Chicago. Time: Dec. 5-10, 1954.

American Board of Dermatology and Syphilology

Nelson Paul Anderson, President, 2007 Wilshire Blvd., Los Angeles 5.
Anthony C. Cipollaro, Secretary, 129 E. 52d St., New York 22.

American Dermatological Association

Richard S. Weiss, President, 3720 Washington Blvd., St. Louis.
J. Lamar Callaway, Secretary, Duke Hospital, Durham, N. C.
Place: Bellevue-Biltmore, Bellaire, Fla. Time: April 17-21, 1955.

Society for Investigative Dermatology

Clarence S. Livingood, President, Henry Ford Hospital, Detroit 2.
Herman Beerman, Secretary, 255 S. 17th St., Philadelphia 3.
Place: Atlantic City, N. J. Time: June 4-5, 1955.

SECTIONAL

Central States Dermatological Association

Herbert H. Johnson, Jr., President, 10515 Carnegie Ave., Cleveland 6.
Benjamin P. Persky, Secretary, 2060 E. 9th St., Cleveland 15.

New England Dermatological Society

E. Myles Standish, President, 85 Jefferson Ave., Hartford, Conn.
Joseph Goodman, Secretary, 375 Commonwealth Ave., Boston.
Place: New Haven Hospital, New Haven, Conn., and Massachusetts General and Boston City hospitals, Boston, (in alternation).

Pacific Dermatologic Association

Stephen T. Parker, President, 1215 4th Ave., Seattle.
Ben A. Newman, Secretary, 436 N. Roxbury Dr., Beverly Hills, Calif.

Pacific Northwest Dermatological Society

Thomas S. Saunders, President, Medical Arts Bldg., Portland 5, Ore.
Leon F. Ray, Secretary, 628 Medical Dental Bldg., Portland 5, Ore.
Time: Third Thursday of May and October.

Rocky Mountain Dermatologic Society

William J. Morginson, President, 141 E. 2nd St., Salt Lake City.
Thomas W. Moffatt, Secretary, 1801 High St., Denver.

Southeastern Dermatological Association

C. M. Hamilton, President, Nashville, Tenn.
Ray O. Noojin, President-elect, Birmingham, Ala.
Adolph B. Loveman, Secretary, Louisville, Ky.
Vonnie Hall, Secretary-elect, Memphis, Tenn.

Southern Medical Association, Section on Dermatology and Syphilology

William L. Dobes, Chairman, 478 Peachtree St., N.E., Atlanta 3, Ga.
Ray O. Noojin, Secretary, 620 S. 20th St., Birmingham, Ala.
Place: St. Louis. Time: Nov. 8-11, 1954.

Southwestern Dermatological Society

Samuel J. Jelso, President, Medical Arts Square, Albuquerque, N. Mex.
Robert H. Snapp, Secretary, 550 W. Thomas Rd., Phoenix, Ariz.

STATE

Alabama Dermatologic Society

Irving D. London, President, 746 Adams Ave., Montgomery.
Abraham I. Perley, Secretary, 2030 11th Ave. S., Birmingham.
Place: Jefferson-Hillman Hospital, Birmingham. Time: Third Monday of each month, September to June.

Arkansas' Dermatological Society

Davis W. Goldstein, Chairman, Cooper Clinic, Fort Smith.
Ray Fulmer, Secretary, 1121 Donaghey Building, Little Rock.

California Medical Association, Scientific Assembly, Dermatology and Syphilology Section

Edward A. Levin, Chairman, 450 Sutter St., San Francisco.
R. Raymond Allington, Secretary, 3115 Webster St., Oakland 9.

Connecticut State Medical Society, Section on Dermatology

Albert Levenson, President, Bridgeport.
Ellwood C. Weise, Jr., Secretary, Bridgeport.
Place: New Haven.

Florida Society of Dermatology and Syphilology

Hollis F. Garrard, President, 401 Ingraham Building, Miami 32.
Joseph Farrington, Secretary, Greenleaf Building, Jacksonville 2.

Hawaii Dermatological Society

Harry L. Arnold Jr., Secretary, 881 S. Hotel St., Honolulu 53.

Indiana State Dermatological Society

Milton Gustafson, President, 808 W. Jackson St., Muncie.
Boynton H. Booth, Secretary, 910 Hume-Mansur Building, Indianapolis.

Louisiana Dermatologic Society

James W. Burks, President, 921 Canal St., New Orleans.
Arturo N. Alvarado, Secretary, 1712 Pere Marquette Building, New Orleans.
Place: Louisiana State Charity Hospital, New Orleans. Time: Third Sunday of each month.

Massachusetts Medical Society, Section on Dermatology and Syphilology

Alfred Hollander, Chairman, 458 Bridge St., Springfield 3.
William R. Hill, Secretary, 520 Commonwealth Ave., Boston 15.
Place: Hotel Statler, Boston.

Medical Society of the State of New York, Section on Dermatology and Syphilology

John G. Copeland, Chairman, Albany.
Joseph J. Hallett, Secretary, Rochester.

Michigan State Medical Society Section on Dermatology and Syphilology

C. J. Courville, Chairman, 1202 Maccabees Building, Detroit 2.
Coleman Mopper, Secretary, 14633 E. 7 Mile near Gratiot, Detroit 2.

Minnesota Dermatological Society

Elmer M. Rusten, President, 78 S. 9th St., Minneapolis 2.
Elmer M. Hill, Secretary, Medical Arts Building, Minneapolis 2.

New Jersey Dermatological Society

Emanuel Satulsky, President, Elizabeth.
Seymour L. Hanfling, Secretary, East Orange.
Place: Newark Academy of Medicine, 91 Lincoln Park, Newark. Time: Second Tuesday of alternate months.

Oklahoma Dermatological Association

Hervey A. Foerster, President, 1220 N. Walker, Oklahoma City.
William G. McCreight, Secretary, 525 N.W. 11th St., Oklahoma City.

Rhode Island Dermatological Society

Vincent J. Ryan, President, Providence.
Arthur B. Kern, Secretary, Providence.

Texas Dermatological Society

Paul W. Power, President, Waco.
Thomas L. Shields, Secretary, 1216 Pennsylvania Ave., Fort Worth.
Place: Rotating. Time: Spring, coincident with Texas State Medical Association; fall, October.

Wisconsin Dermatological Society

Kurt Wiener, President.
Donald Ruch, Secretary, 208 E. Wisconsin Ave., Milwaukee 2.

LOCAL

Baltimore-Washington Dermatological Society

Israel Zeligman, Chairman, 1109 N. Calvert St., Baltimore 2.
Raymond C. V. Robinson, Secretary, 1001 St. Paul St., Baltimore 2.
Place: Baltimore and Washington. Time: Third Thursday of each month, in alternate cities, October to May.

Bronx Dermatological Society

Rudolf L. Baer, President, 962 Park Ave., New York.
Henry Silver, Secretary, 290 W. End Ave., New York.
Place: Academy of Medicine. Time: Third Thursday of every month, October to May.

Brooklyn Dermatological Society

C. B. Locasto, President, 1 Hanson Place, Brooklyn 17.
Frank D. Jennings, Jr., Secretary, 361 Clinton Ave., Brooklyn 5.
Place: Brooklyn Hospital Dispensary, Ashland Place, Brooklyn. Time: Third Monday of each month, October to May.

Buffalo-Rochester Dermatological Society

Hans Neuberg, President, 261 Alexander St., Rochester, N. Y.
Frank A. Dolce, Secretary, 468 Delaware Ave., Buffalo.
Place: Edward J. Meyer Memorial Hospital, Buffalo, and Strong Memorial Hospital, Rochester. Time: Second Tuesday of every month, October to May, inclusive.

Central New York Dermatological Society

Francis J. Fagan, President, 65 2nd St., Troy.
Julius Voehl, Secretary, 713 E. Genesee St., Syracuse.

Chicago Dermatological Society

Julius E. Ginsberg, President, 8501 S. Cottage Grove Ave.
Irene Neuhauser, Secretary, 7 W. Madison, St.
Place: Chicago. Time: Third Wednesday of each month except June, July, August, and September.

Cincinnati Dermatological Society

Carey C. Barrett, President, 200 N. Upper St., Lexington, Ky.
Donald J. Birmingham, Secretary, Occupational Health Field Hdqtrs., Public Health Service, 1014 Broadway, Cincinnati.
Place: Cincinnati General Hospital. Time: 8:00 p. m., first Wednesday of each month, October to May.

Cleveland Dermatological Society

Gerard DeOreo, President, 10515 Carnegie Ave., Cleveland 6.
Benjamin P. Persky, Secretary, 2060 E. 9th St., Cleveland 15.

Dallas Dermatological Society

Bedford Shelmire, President, 1410 Medical Arts Building.
D. Shelton Blair, 304 Medical Arts Building.
Place: Medical Arts Building. Time: Third Wednesday of each month.

Detroit Dermatological Society

Charles J. Courville, President, 1202 Maccabees Building (2).
Loren W. Shaffer, President-elect, 1553 Woodward Ave. (26)
Coleman Mopper, Secretary, 302 Holbrook Building (12).

Kansas City Dermatological Society

David B. Morgan, President, 520 Professional Bldg., Kansas City.
Frank X. Dwyer, Secretary, 231 W. 47th St., Kansas City.
Place: University of Kansas Medical Center, Kansas City, Kan. Time: 10:00 a. m., second Sunday of each month, from October through June.

Long Island Dermatological Society

Albert Schur, President, 1323 Cornaga Ave., Far Rockaway, L. I.
Kurt Bardach, President-elect, 144-35 Northern Blvd., Flushing.
Conrad Stritzler, Secretary, 90-26 148th St., Jamaica 2, N. Y.
Place: Queens General Hospital, Jamaica, N. Y. Time: Second Tuesday of each month, 8:00 p. m.

Los Angeles Dermatological Society

Anker K. Jensen, President, 1052 W. 6th St., Los Angeles.
Louis H. Winer, Secretary, 9915 Santa Monica Blvd., Beverly Hills.
Place: Good Hope Clinical Association. Time: Second Tuesday of each month, October to May.

Manhattan Dermatologic Society

Thomas N. Graham, President, 118 E. 61st St., (21).
George M. Lewis, Secretary, 66 E. 66th St. (21).
Place: Each member's office, in rotation. Time: 8:00 p. m., second Tuesday of each month.

Metropolitan Dermatological Society

Anthony N. Domonkos, President, 115 E. 61st St., New York 21.
Charles F. Post, Secretary, 4 Wilsey Square, Ridgewood, N. J.
Place: Offices of members. Time: Third Monday of each month, October to May.

Metropolitan Dermatological Society of Chicago

Franz Baumann, President, 30 N. Michigan Ave., Chicago 2.
Tibor Benedek, Secretary, 25 E. Washington St., Chicago 2.
Place: Chicago, alternating in the Services of the Fellows. Time: Second Wednesday, 10:00 a. m., from October to May.

Metropolitan Dermatological Society of Los Angeles

Fred P. Feldman, President, 436 N. Roxbury Dr., Beverly Hills.
Harold Price, Secretary, 4418 Vineland Ave., North Hollywood.
Time: Fourth Tuesday of each month, October through May.

Metropolitan Miami Dermatoloigcal Society

Wiley Sams, President, 25, S.E. 2nd Ave., Miami, Fla.
Bruce M. Esplin, Secretary, 602 Huntington Building, Miami, Fla.
Place: Jackson Memorial Hospital, Miami, Fla. Time: Last Thursday of each quarter.

Montreal Dermatological Society

J. P. Foisy, President, 1871 Sherbrooke St., E.
P. A. Turgeon, Secretary, 837 Cherrier St.
Place: Royal Victoria Hospital, Notre Dame Hospital, Montreal General Hospital, and other hospitals. Time: October, February, and April.

New York Academy of Medicine, Section of Dermatology and Syphilology

Timothy J. Riordan, Chairman.
Wilbert Sachs, Secretary.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: First Tuesday of each month.

New York Dermatological Society

John C. Graham, President.
Gerald F. Machacek, Secretary.
Place: New York. Time: Fourth Tuesday of each month.

Omaha Dermatological Society

Olin J. Cameron, President, 1520 Medical Arts Bldg.
George F. Pinne, Secretary, 453 Aquila Ct.

Philadelphia Dermatological Society

Bertram Shaffer, President, 1825 Pine St (3).
Lewis M. Johnson, Secretary, 203 N. Lime St., Lancaster, Pa.
Place: Philadelphia hospitals. Time: Third Friday of each month except June, July, and August.

Pittsburgh Dermatological Society

M. H. Applbaum, President, 530 McKean Ave., Charleroi.
Saul R. Bergad, Secretary, 4048 Jenkins Arcade.
Place: Falk Clinic, 3601 Fifth Ave. Time: Third Thursday of each month.

San Francisco Dermatological Society

Edward A. Levin, President, 450 Sutter St.
Max E. Krause, Secretary, 400 29th St., Oakland, Calif.

St. Louis Dermatological Society

Newell W. Schlueter, President, 634 N. Grand Blvd. (3).
Morris Moore, Secretary, 3427 Washington Blvd.
Place: Barnard Free Skin and Cancer Hospital. Time: 8:00 p. m., third Monday of each month, October to May.

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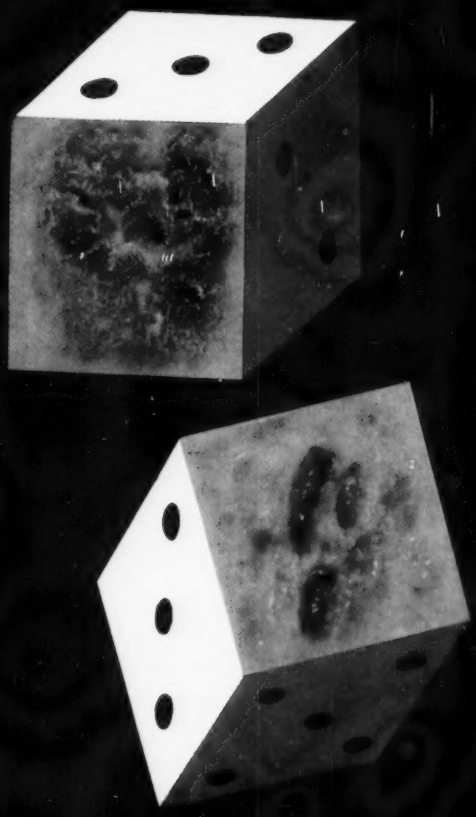

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References:

1. Perrin, S. R., and Halpern, A.: A Comparative Study of the Use of Hydrophilic Absorption Ointment Bases, J. Invest. Dermat. *16*:7, 1951.
2. Perrin, S. R.: Clinical Safety of Polysorb, Postgrad. Med. *8*:485, 1950.

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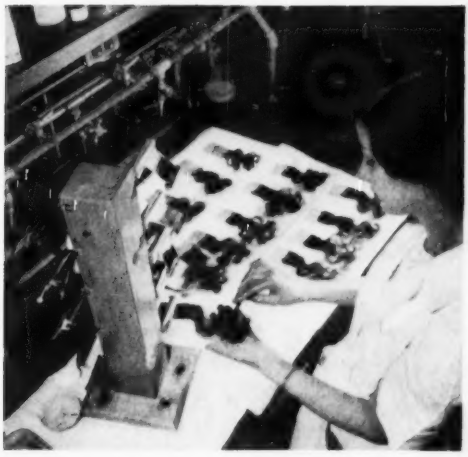

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1. Ellis, C. C., and others: The Treatment of Psoriasis with Liquor Carbonis Detergens. J. Invest. Dermat. 10:455, 1948.

2. Sulzberger, M. B., and Wolf, J. Dermatology. Essentials of Diagnosis and Treatment. Chicago, Year Book Publishers, Inc., 1952, p. 323.

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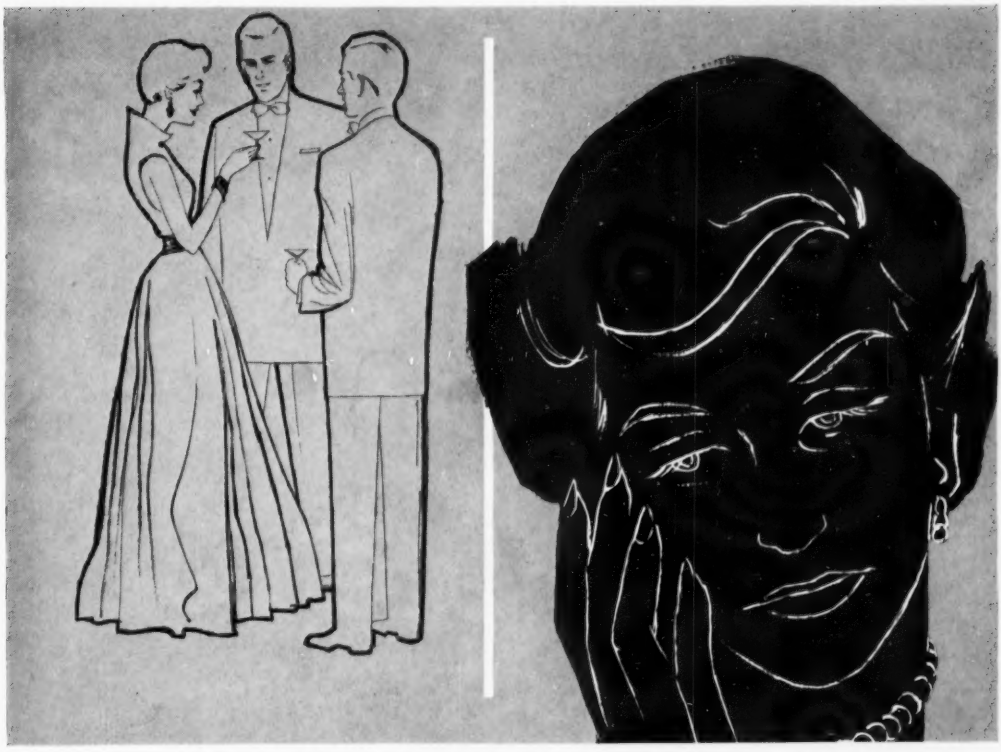

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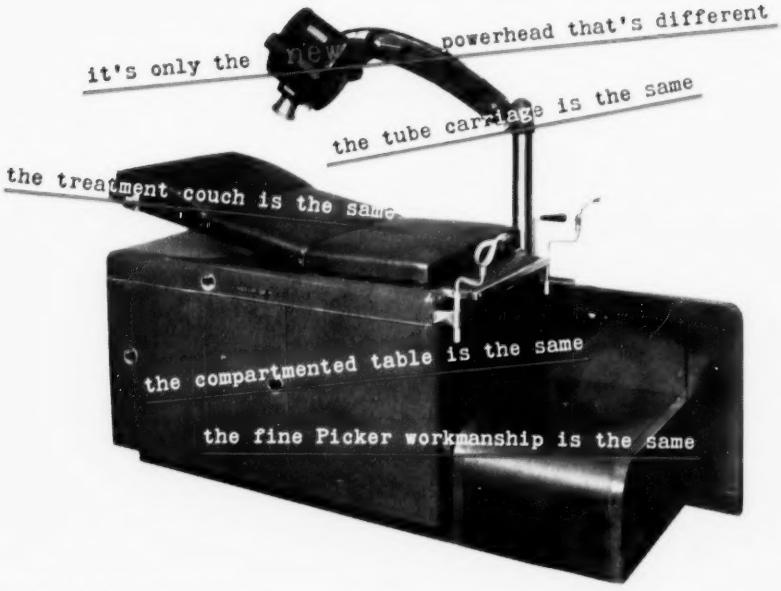
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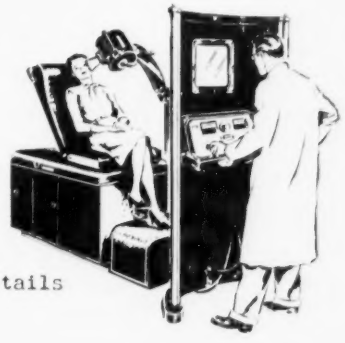

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